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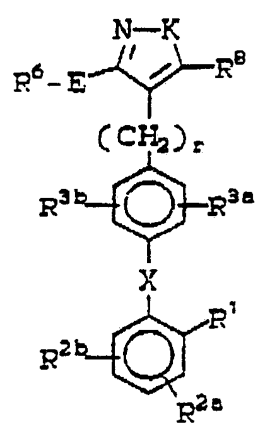
(54) Title: SUBSTITUTED PYRAZOLES, ISOXAZOLES AND ISOTHIAZOLES



(I)

(57) Abstract

Substituted pyrazoles, isoxazoles and isothiazoles of formula (I) are angiotensin II antagonists, and are useful in the treatment of hypertension, ocular hypertension and certain CNS disorders.

TITLE OF THE INVENTION

SUBSTITUTED PYRAZOLES, ISOXAZOLES AND ISOTHIAZOLES

SUMMARY OF THE INVENTION

This is a continuation-in-part of copending application S.N. 501,469 filed March 30, 1990 (allowed).

This invention relates to novel substituted pyrazole, isoxazole and isothiazole compounds and derivatives thereof which are useful as angiotensin II antagonists in the treatment of elevated blood pressure and congestive heart failure and in the treatment of ocular hypertension.

The compounds of this invention also have central nervous system (CNS) activity. They are useful in the treatment of cognitive dysfunctions including Alzheimer's disease, amnesia and senile dementia. These compounds also have anxiolytic and antidepressant properties and are therefore, useful in the relief of symptoms of anxiety and tension and in the treatment of patients with depressed or dysphoric mental states.

In addition, these compounds exhibit antidopaminergic properties and are thus useful to treat disorders that involve dopamine dysfunction such as schizophrenia.

BACKGROUND OF THE INVENTION

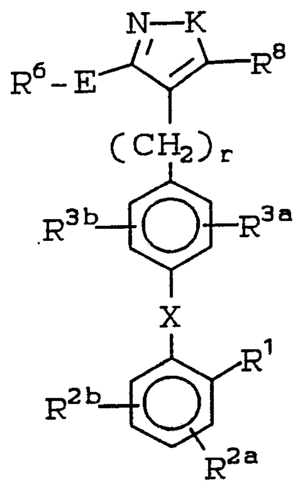
Renin-angiotensin system (RAS) plays a central role in the regulation of normal blood pressure and seems to be critically involved in hypertension development and maintenance as well as congestive heart failure. Angiotensin II (A II), an octapeptide hormone, is produced mainly in the blood during the cleavage of angiotensin I by angiotensin converting enzyme (ACE) localized on the endothelium of blood vessels of lung, kidney, and many other organs, and is the end product of the RAS. A II is a powerful arterial vasoconstrictor that exerts its action by interacting with specific receptors present on cell membranes. One of the possible modes of controlling the RAS is angiotensin II receptor antagonism. Several peptide analogs of A II are known to inhibit the effect of this hormone by

competitively blocking the receptors, but their experimental and clinical applications have been limited by partial agonist activity and lack of oral absorption [M. Antonaccio. Clin. Exp. Hypertens. A4, 27-46 (1982); D. H. P. Streeten and G. H. Anderson, Jr. - Handbook of Hypertension, Clinical Pharmacology of Antihypertensive Drugs, ed. A. E. Doyle, Vol. 5, pp. 246-271, Elsevier Science Publisher, Amsterdam, The Netherlands, 1984].

Recently, several non-peptide compounds have been described as A II antagonists. Illustrative of such compounds are those disclosed in U.S. Patents 4,207,324; 4,340,598; 4,576,958; 4,582,847; and 4,880,804; in European Patent Applications 028,834; 245,637; 253,310; 291,969; 323,841; and 324,377; and in articles by A.T. Chiu, et al. [Eur. J. Pharm. Exp. Therap, 157, 13-21 (1988)] and by P.C. Wong, et al. [J. Pharm. Exp. Therap, 247, 1-7(1988)]. All of the U.S. Patents, European Patent Applications 028,834 and 253,310 and the two articles disclose substituted imidazole compounds which are generally bonded through a lower alkyl bridge to a substituted phenyl. European Patent Application 245,637 discloses derivatives of 4,5,6,7-tetrahydro-2H-imidazo[4,5-c]-pyridine-6-carboxylic acid and analogs thereof as antihypertensive agents.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention have the general formula (I):



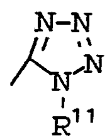
(I)

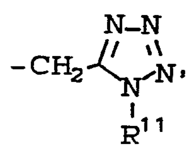
wherein:

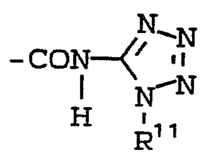
K is O, S or NR^7;

R^1 is
(a) $-CO_2R^5$,
(b) $-SO_3R^5$,
(c) $-NHSO_2(C_1-C_4\text{-polyfluoroalkyl})$,
(d) $-PO(OR^5)_2$,
(e) $-SO_2-NH-R^9$,
(f) $-CONHOR^5$,
(g) $-\underset{R^9}{\overset{OH}{C}}-\underset{OR^5}{\overset{O}{\overset{\|}{P}}}-OR^5$,

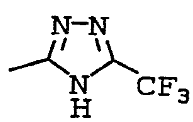
(h) $-SO_2NH$-heteroaryl,
(i) $-CH_2SO_2NH$-heteroaryl,
(j) $-SO_2NH-CO-R^{23}$,
(k) $-CH_2SO_2NH-CO-R^{23}$,
(l) $-CONH-SO_2R^{23}$,
(m) $-CH_2CONH-SO_2R^{23}$,
(n) $-NHSO_2NHCO-R^{23}$,
(o) $-NHCONHSO_2-R^{23}$,

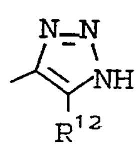
(p) ,

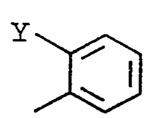
(q) ,

(r) 

(s) $-CONHNHSO_2CF_3$,

(t) 

(u) 

(v) 

wherein Y is

(1) $-CO_2R^4$,
(2) $-SO_3R^5$,
(3) $-NHSO_2CF_3$,
(4) $-PO(OR^5)_2$,
(5) $-SO_2NHR^9$,
(6) 1H-tetrazol-5-yl.

(x) $-\overset{\displaystyle O}{\overset{\|}{\underset{\displaystyle OR^5}{\underset{|}{P}}}}-R^{23}$ or

(y) $-NH\overset{\displaystyle O}{\overset{\|}{C}}-\overset{\displaystyle O}{\overset{\|}{\underset{\displaystyle OR^5}{\underset{|}{P}}}}-R^{23}$

wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted five or six membered aromatic ring comprising from 1 to 3 heteroatoms selected from the group consisting of O, N and S and wherein the substituents are members selected from the group consisting of -OH, -SH, $-C_1-C_4$-alkyl, $-C_1-C_4$-alkoxy, $-CF_3$, halo, $-NO_2$, $-CO_2H$, $-CO_2-C_1-C_4$-alkyl, $-NH_2$, $NH(C_1-C_4$-alkyl), $-N(C_1-C_4$-alkyl$)_2$ and a fused benzo group;

R^{2a} and R^{2b} are independently

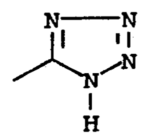
(a) H,
(b) halo,
(c) NO_2,
(d) NH_2,
(e) C_1-C_4-alkylamino,
(f) di-(C_1-C_4-alkyl)amino
(g) SO_2NHR^9,

(h) CF_3,
(i) C_1-C_4-alkyl, or
(j) C_1-C_4-alkoxy;

R^{3a} is
(a) H,
(b) halo,
(c) C_1-C_6-alkyl,
(d) C_1-C_6-alkoxy, or
(e) C_1-C_6-alkoxy-C_1-C_4-alkyl;

R^{3b} is
(a) H,
(b) halo,
(c) NO_2,
(d) C_1-C_6-alkyl,
(e) C_2-C_6-alkanoyloxy,
(f) C_3-C_6-cycloalkyl,
(g) C_1-C_6-alkoxy,
(h) $-NHSO_2R^4$,
(i) hydroxy-C_1-C_4-alkyl,
(j) aryl-C_1-C_4-alkyl,
(k) C_1-C_4-alkylthio,
(l) C_1-C_4-alkylsulfinyl,
(m) C_1-C_4-alkylsulfonyl,
(n) NH_2,
(o) C_1-C_4-alkylamino,
(p) di(C_1-C_4-alkyl)amino,
(q) CF_3,
(r) $-SO_2-NHR^9$,
(s) aryl or
(t) furyl;

wherein aryl is phenyl or naphthyl either unsubstituted or substituted with one, two or three substituents selected from the group consisting of halo, C_1-C_4-alkyl, C_1-C_4-alkoxy, NO_2, CF_3, C_1-C_4-alkylthio, OH, NH_2, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl$)_2$, $-CO_2H$, $-CO_2$-C_1-C_4-alkyl, C_1-C_4-polyfluoroalkyl, C_3-C_6-polyfluorocycloalkyl, and


;

R^4 is H, C_1-C_6-alkyl, aryl or $-CH_2$-aryl;

R^5 is H, $-\overset{R^4}{\overset{|}{C}}H-O-\overset{O}{\overset{\|}{C}}-R^{4a}$, wherein R^{4a} is C_1-C_6-alkyl, aryl, or $-CH_2$-aryl;

E is a single bond, $-NR^{13}(CH_2)_s-$, $-S(O)_x(CH_2)_s-$ where x is 0 to 2 and s is 0 to 5, -CH(OH)-, -O-, -CO-;

R^6 is

C_1-C_6-alkyl, C_2-C_5-alkenyl or C_2-C_5-alkynyl each of which can be substituted with a substituent selected from the group consisting of aryl, C_3-C_7-cycloalkyl, halo, -OH, $-CF_3$, $-CCl_3$, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl$)_2$, $-NH-SO_2R^4$, $-COOR^4$, $-SO_2NHR^9$, C_1-C_4-alkoxy, or C_1-C_4-alkyl-S;

R^7 is (a) -H,

(b) C_1-C_{10}-alkyl;

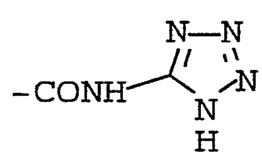
(c) substituted C_1-C_{10}-alkyl in which one or more substituent(s) is selected from

- (1) I, Br, Cl, or F,
- (2) hydroxy,
- (3) C_1-C_{10}-alkoxy,
- (4) C_1-C_5-alkoxycarbonyl,
- (5) C_1-C_4-alkylcarbonyloxy,
- (6) C_3-C_8-cycloalkyl,
- (7) aryl,
- (8) heteroaryl,
- (9) C_1-C_{10}-alkyl-$S(O)_p$ in which p is 0 to 2,
- (10) C_3-C_8-cycloalkyl-$S(O)_p$,
- (11) aryl-$S(O)_p$,
- (12) oxo,
- (13) carboxy,
- (14) NR^9R^9,
- (15) C_1-C_5-alkylaminocarbonyl,
- (16) di(C_1-C_5-alkyl)aminocarbonyl,
- (17) cyano;
- (18) $-OCONR^{22}R^{23}$
- (19) $NR^{22}COR^{23}$
- (20) $-NR^{22}CO_2R^{23}$
- (21) $-NR^{22}CONR^{22}R^{23}$
- (22) $-NR^{22}CON$  L
- (23) -OCON  L wherein L is a single bond, CH_2, O, $S(O)_p$ or NR^9

(d) C_2-C_{10}-alkenyl,
(e) C_2-C_{10}-alkynyl,
(f) C_3-C_8-cycloalkyl,
(g) substituted C_3-C_8-cycloalkyl or substituted C_3-C_8-cycloalkyl-C_1-C_4-alkyl having one or more substituents selected from the group:
    (1) Cl, Br, F, or I
    (2) hydroxy,
    (3) C_1-C_6-alkyl,
    (4) C_1-C_6-alkoxy,
    (5) C_1-C_4-alkylcarbonyloxy,
    (6) C_1-C_5-alkoxycarbonyl,
    (7) carboxy,
    (8) oxo,
    (9) C_1-C_5-alkylaminocarbonyl,
    (10) di(C_1-C_5-alkyl)aminocarbonyl,
    (11) C_1-C_4-alkylcarbonyl, and
    (12) aryl,
(h) aryl, or
(i) heteroaryl;

R^8 is
(a) hydrogen,
(b) -OH,
(c) $-NH_2$,
(d) -NH(C_1-C_4-alkyl) wherein the alkyl is unsubstituted or substituted with CO_2R^4,
(e) -N(C_1-C_4-alkyl$)_2$ wherein one or both of the alkyl groups can be substituted with CO_2R^4,
(f) $-NHCO_2$-C_1-C_4-alkyl,
(g) $-NHSO_2$-aryl,
(h) $-NHSO_2$-heteroaryl,

(i) $-NHSO_2(C_1-C_4$-polyfluoroalkyl),
(j) $-CO_2H$,
(k) $-CO_2R^5$,
(l) halo,
(m) $-CONHSO_2$-aryl,
(n) $-CONHSO_2$-heteroaryl,
(o) $-CONHSO_2-C_1-C_4$-alkyl, either unsubstituted or substituted with aryl, $-NH_2$, $-NH(C_1-C_4$-alkyl), $-N(C_1-C_4$-alkyl$)_2$; -OH, $-CO_2H$, or $CO_2(C_1-C_4$-alkyl),
(p) $-CONHSO_2(C_1-C_4$-polyfluoroalkyl),
(q) $-CH_2OH$,
(r) $-CH_2OCOR^4$,
(s) $-O-C_1-C_4$-alkyl,
(t) $-S(O)_x-C_1-C_4$-alkyl, either unsubstituted or substituted with aryl, $-NH_2$, $-NH(C_1-C_4$-alkyl), $-N(C_1-C_4$- alkyl)2, -OH, $-CO_2H$, or $CO_2(C_1-C_4$-alkyl),
(u) $-SO_2NHR^{21}$,
(v) -CN,
(w) tetrazol-5-yl,

(x) ,

(y) $-CH_2CO_2R^4$;

R^9 is H, C_1-C_5-alkyl, aryl or $-CH_2$-aryl;
R^{10} is H, C_1-C_4-alkyl;

R^{11} is H, C_1-C_6-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy alkyl, or $-CH_2-C_6H_4R^{20}$;

R^{12} is $-CN$, $-NO_2$, $-CO_2R^4$, or $-CF_3$;

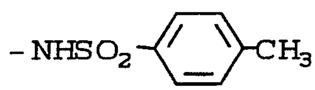
R^{13} is H, C_2-C_4-alkanoyl, C_1-C_6-alkyl, allyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{14} is H, C_1-C_8-alkyl, C_1-C_8-perfluoroalkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

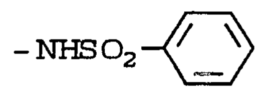
R^{15} is H, C_1-C_6-alkyl;

R^{16} is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{17} is $-NR^9R^{10}$, $-OR^{10}$, $-NHCONH_2$, $-NHCSNH_2$,



or



;

R^{18} and R^{19} are independently C_1-C_4-alkyl or taken together are $-(CH_2)_q-$ where q is 2 or 3;

R^{20} is H, $-NO_2$, $-NH_2$, $-OH$ or $-OCH_3$;

R^{21} is
(a) -CO-aryl,
(b) $-CO-C_1$-C_4-alkyl,
(c) $-COCF_3$,
(d) -CO-heteroaryl, or
(e) heteroaryl;

R^{23} is
(a) aryl,
(b) heteroaryl,
(c) C_3-C_7-cycloalkyl,
(d) C_1-C_6-alkyl either unsubstituted or substituted with aryl, heteroaryl, -OH, -SH, C_1-C_4-alkyl, C_3-C_7-cycloalkyl, $-O(C_1$-C_4-alkyl),

$-S(C_1-C_4\text{-alkyl})$, $-CF_3$, halo, $-NO_2$, $-CO_2H$, $CO_2-C_1-C_4\text{-alkyl}$, $-NH_2$, NHaryl, $N(\text{aryl})_2$, $-NH(C_1-C_4\text{-alkyl})$, $-N(C_1-C_4\text{-alkyl})_2$, $-PO_3H$, $-PO(OH)(O-C_1-C_4\text{-alkyl})$, or $-N(CH_2CH_2)_2L$ wherein L is single bond, $-CH_2-$, $-O-$, $-S(O)p$, or NR^9; and

(e) polyfluoro-C_1-C_4-alkyl;

X is

(a) a carbon-carbon single bond,

(b) -CO-,

(c) -O-,

(d) -S-,

(e) $-\underset{\substack{|\\R^{13}}}{N}-$,

(f) $-CO\underset{\substack{|\\R^{15}}}{N}-$,

(g) $-\underset{\substack{|\\R^{15}}}{N}CO-$,

(h) $-OCH_2-$,

(i) $-CH_2O-$

(j) $-SCH_2-$,

(k) $-CH_2S-$,

(l) $-NHC(R^9)(R^{10})$,

(m) $-NR^9SO_2-$,

(n) $-SO_2NR^9-$,

(o) $-C(R^9)(R^{10})NH-$,

(p) -CH=CH-,

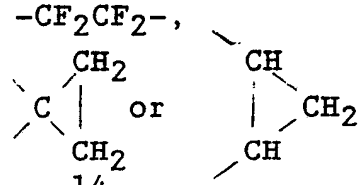
(q) -CF=CF-,

(r) -CH=CF-,

(s) $-CF=CH-$,

(t) $-CH_2CH_2-$,

(u) $-CF_2CF_2-$,

(v) 

(w) $-\overset{OR^{14}}{\overset{|}{C}H}-$,

(x) $-\overset{OCOR^{16}}{\overset{|}{C}H}-$,

(y) $-\overset{NR^{17}}{\overset{\|}{C}}-$, or

(z) $\overset{R^{18}O \quad OR^{19}}{\diagdown\ \diagup}$ $-C-$;

Z is O, NR^{13} or S;

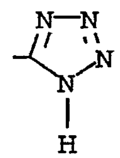
r is 1 or 2; and

the pharmaceutically acceptable salts thereof.

The terms "alkyl", "alkenyl", "alkynyl: and the like include both the straight chain and branched chain species of these generic terms wherein the number of carbon atoms in the species permit. Unless otherwise noted, the specific names for these generic terms shall mean the straight chain species. For example, the term "butyl" shall mean the normal butyl substituent, n-butyl. The term "halo" means Cl, Br, I or F.

One embodiment of the compounds of formula (I) are those compounds wherein K is -O-.

A class of compounds within this embodiment is that wherein:

R^1 is -COOH , $-NH-SO_2CF_3$,

$-SO_2NH-CO-R^{23}$, $-SO_2NH$-heteroaryl, $-SO_2NH$ aryl, or $-CONHSO_2R^{23}$,

R^{2a} and R^{2b} are H, F, Cl, CF_3, C_1-C_4-alkyl or C_1-C_4-alkoxy;

R^{3a} is H, F or Cl;

R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_1-C_4-alkoxy, $-COOCH_3$, $-COOC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1$-C_4-alkyl$)_2$ or $-NH-SO_2CH_3$;

E is a single bond, -O- or -S-;

R^6 is

(a) C_1-C_5-alkyl either unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF_3, CCl_3, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$ or phenyl;

(b) C_2-C_5-alkenyl or C_2-C_5-alkynyl;

X is a C-C single bond; and,

r is one.

In a preferred class of this embodiment are those compounds wherein:

E is a single bond or -S-;

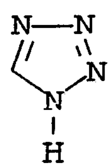
r is one,

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H;

R^6 is n-propyl, n-butyl, $-CH_3$, $-CH_2CH_3$, or $-CH_2-S-CH_3$;

R^8 is $-CO_2R^5$, $-CONHSO_2$aryl, $-CONHSO_2(C_1-C_4$-alkyl), or CONH-SO_2-cyclopropyl, $-NHSO_2(C_1-C_4$-polyfluoroalkyl), $-S(O)_x-(C_1-C_4$-alkyl)-aryl, $-NHSO_2$aryl, or $-NHSO_2$-heteroaryl;

R^1 is -COOH, $-SO_2$NH-heteroaryl, $-SO_2$NH-aryl,


, $-CONHSO_2R^{23}$

$-NH-SO_2-CF_3$, or SO_2NHCOR^{23};

R^{23} is aryl, $-N(\text{aryl})_2$, C_3-C_7-cycloalkyl, C_1-C_6 alkyl, either unsubstituted or substituted with 1) C_3-C_7 cycloalkyl, 2) polyfluoro, or 3) two aryl groups, and

X is a single bond.

Exemplifying this class are the following compounds:

(1) Ethyl 3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]isoxazole-5-carboxylate

(2) 3-Butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]isoxazole-5-carboxylic acid

(3) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-butylisoxazole-5-carboxylic acid

(4) 3-Butyl-4-[[2'-[N-(trifluoroacetyl)sulfamoyl]biphenyl-4-yl]methyl]isoxazole-5-carboxylic acid

(5) 3-Butyl-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isoxazole-5-carboxylic acid

(6) 3-Butyl-4-[[2'-[N-(cyclopropanecarbonyl)-sulfamoyl]biphenyl-4-yl]methyl]isoxazole-5-carboxylic acid

(7) 4-[[2'-[N-(Diphenylacetyl)sulfamoyl]-biphenyl-4-yl]methyl]-3-propylisoxazole-5-carboxylic acid

(8) 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl] methyl]isoxazole-5-carboxylic acid

(9) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-propylisoxazole-5-carboxylic acid

(10) 4-[[2'-[N-(Cyclopropanecarbonyl)sulfamoyl]-biphenyl-4-yl]methyl]-3-propylisoxazole-5-carboxylic acid

(11) 3-Propyl-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isoxazole-5-carboxylic acid

(12) 5-[N-(Benzenesulfonyl)carbamoyl]-3-butyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isoxazole

(13) 3-Butyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-isoxazole

(14) 3-Butyl-5-(pentafluoroethanesulfonamido)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isoxazole

(15) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-butyl-5-(trifluoromethanesulfon-amido)isoxazole

(16) 3-Butyl-4-[[2'-[N-(cyclopropanecarbonyl)-sulfamoyl]biphenyl-4-yl]methyl-5-(trifluoro-methanesulfonamido)isoxazole

(17) 3-Butyl-5-(trifluoromethanesulfonamido)-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isoxazole

(18) 3-Propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-isoxazole

(19) 5-(Pentafluoroethanesulfonamido)-3-propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isoxazole

(20) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-propyl-5-(trifluoromethanesulfon-amido)isoxazole

(21) 4-[[2'-[N-(Cyclopropanecarbonyl)sulfamoyl]-biphenyl-4-yl]methyl]-3-propyl-5-(trifluoro-methanesulfonamido)isoxazole

(22) 3-Butyl-5-(4-chlorobenzylsulfinyl)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isoxazole

(23) 3-Butyl-5-(2-carboxybenzylthio)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isoxazole

(24) 3-Butyl-5-[N-(isopropylsulfonyl)carbamoyl]-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-isoxazole

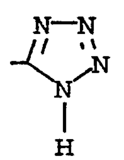
(25) 3-Butyl-5-[N-(cyclopropanesulfonyl)carbamoyl]-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]isoxazole

(26) 3-Butyl-5-(4-fluorobenzenesulfonamido)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-isoxazole

(27) 3-Butyl-5-(3-pyridinesulfonamido)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]isoxazole

Another embodiment of the compounds of formula (I) is that wherein K is S.

A class of compounds within that embodiment are those compounds wherein

R^1 is  , $-NH-SO_2CF_3$, CO_2H,

$-SO_2NH-COR^{23}$, $-SO_2NH$-heteroaryl, $-SO_2NH$-aryl, or $-CONHSO_2R^{23}$;

R^{2a} and R^{2b} are H, F, Cl, CF_3, C_1-C_4-alkyl or C_1-C_4-alkoxy;

R^{3a} is H, F or Cl;

R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_5-C_6-cycloalkyl, $-COOCH_3$, $-COOC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1$-C_4-alkyl$)_2$ or $-NH-SO_2CH_3$;

E is a single bond, -O- or -S-;

R^6 is

(a) C_1-C_5-alkyl either unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF_3, CCl_3, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$ or phenyl;

(b) C_2-C_5-alkenyl or C_2-C_5-alkynyl;

X is a C-C single bond; and,

r is one.

In a preferred class of this embodiment are those compounds wherein:

E is a single bond or -S-;

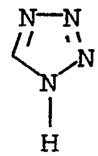
r is one,

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H;

R^6 is n-propyl, n-butyl, $-CH_3$, $-CH_2CH_3$, or $-CH_2-S-CH_3$;

R^8 is $-CO_2R^5$, $-CONHSO_2$aryl, $-CONHSO_2$-(C_1-C_4-alkyl), $-CONHSO_2$-cyclopropyl, $-NHSO_2$(C_1-C_4-polyfluoroalkyl), $S(O)_x$-(C_1-C_4-alkyl)aryl, $-NHSO_2$-aryl, or $-NHSO_2$-heteroaryl;

R^1 is -COOH, SO_2NH-heteroaryl, $-SO_2NH$-aryl,

, $-CONHSO_2R^{23}$

$NH-SO_2-CF_3$, or $-SO_2NHCOR^{23}$;
R^{23} is aryl, polyfluoro-C_1-C_4 alkyl, C_3-C_7 cycloalkyl or C_1-C_4 alkyl(aryl)$_2$; and

X is a single bond.

Exemplifying this class are the following compounds:

(1) Ethyl 3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]isothiazole-5-carboxylate
(2) 3-Butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]isothiazole-5-carboxylic acid
(3) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-butylisothiazole-5-carboxylic acid
(4) 3-Butyl-4-[[2'-[N-(trifluoroacetyl)sulfamoyl]-biphenyl-4-yl]methyl]isothiazole-5-carboxylic acid
(5) 3-Butyl-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isothiazole-5-carboxylic acid
(6) 3-Butyl-4-[[2'-[N-(cyclopropanecarbonyl)-sulfamoyl]biphenyl-4-yl]methyl]isothiazole-5-carboxylic acid

(7) 4-[[2'-[N-(Diphenylacetyl)sulfamoyl]biphenyl-4-yl]methyl]-3-propylisothiazole-5-carboxylic acid

(8) 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]isothiazole-5-carboxylic acid

(9) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-propylisothiazole-5-carboxylic acid

(10) 4-[[2'-[N-(Cyclopropanecarbonyl)sulfamoyl]-biphenyl-4-yl]methyl]-3-propylisothiazole-5-carboxylic acid

(11) 3-Propyl-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isothiazole-5-carboxylic acid

(12) 5-[N-(Benzenesulfonyl)carbamoyl]-3-butyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isothiazole

(13) 3-Butyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-isothiazole

(14) 3-Butyl-5-(pentafluoroethanesulfonamido)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isothiazole

(15) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-butyl-5-(trifluoromethanesulfonamido)isothiazole

(16) 3-Butyl-4-[[2'-[N-(cyclopropanecarbonyl)-sulfamoyl]biphenyl-4-yl]methyl-5-(trifluoromethanesulfonamide)isothiazole

(17) 3-Butyl-5-(trifluoromethanesulfonamido)-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isothiazole

(18) 3-Propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-isothiazole

(19) 5-(Pentafluoroethanesulfonamido)-3-propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isothiazole

(20) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-propyl-5-(trifluoromethanesulfonamido)isothiazole

(21) 4-[[2'-[N-(Cyclopropanecarbonyl)sulfamoyl]-biphenyl-4-yl]methyl]-3-propyl-5-(trifluoromethanesulfonamido)isothiazole

(22) 3-Butyl-5-(4-chlorobenzylsulfinyl)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isothiazole

(23) 3-Butyl-5-(2-carboxybenzylthio)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isothiazole

(24) 3-Butyl-5-[N-(isopropylsulfonyl)carbamoyl]-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-isothiazole

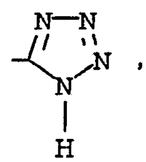
(25) 3-Butyl-5-[N-(cyclopropanesulfonyl)carbamoyl]-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]isothiazole

(26) 3-Butyl-5-(4-fluorobenzenesulfonamido)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-isothiazole

(27) 3-Butyl-5-(3-pyridinesulfonamido)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]isothiazole

Another embodiment of the novel compounds of formula (I) is that wherein $K=NR^7$.

A class of compounds within this embodiment is that wherein:

R^1 is -COOH,  $-NH-SO_2CF_3$,

$-SO_2NHCOR^{23}$, $-SO_2NH$-heteroaryl, $-SO_2NH$-aryl, or $-CONHSO_2R^{23}$;

R^{2a} and R^{2b} are H, F, Cl, CF_3, C_1-C_4-alkyl or C_1-C_4-alkoxy;

R^{3a} is H, F or Cl;

R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_5-C_6-cycloalkyl, $-COOCH_3$, $-COOC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1$-C_4-alkyl$)_2$ or $-NH-SO_2CH_3$;

E is a single bond, -O- or -S-;

R^6 is

(a) C_1-C_5-alkyl either unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF_3, CCl_3, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$ or phenyl;

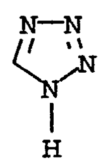
(b) C_2-C_5-alkenyl or C_2-C_5-alkynyl;

R^7 and R^8 are as defined above;

X is a C-C single bond; and,
r is one.

In a preferred class of this embodiment are those compounds wherein:

E is a single bond or -S-;
r is one,
R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H;
R^6 is n-propyl, n-butyl, $-CH_3$, $-CH_2CH_3$, or $-CH_2-S-CH_3$;
R^1 is -COOH, $-SO_2NH$-heteroaryl, $-SO_2NH$-aryl, $-CONHSO_2R^{23}$, $-SO_2NHSO_2R^{23}$



$-NH-SO_2-CF_3$, or $-SO_2NHCOR^{23}$; and
R^7 is H, aryl-C_1-C_{10}-alkyl, polyfluoro-C_1-C_4-alkyl, heteroaryl, or aryl either unsubstituted or substituted with one or two substituents selected from -Cl, $-CF_3$, $-CH_3$, $-OCH_3$ and $-NO_2$;
R^8 is $-CO_2R^5$, $-CONHSO_2$aryl, $-CONHSO_2$-(C_1-C_4-alkyl),$-CONHSO_2$-cyclopropyl,$-NHSO_2$-(C_1-C_4- polyfluoroalkyl),$-S(O)_x$-(C_1-C_4-alkyl)-aryl, or $-NHSO_2$-aryl, or $NHSO_2$-heteroaryl;
R^{23} is aryl, $-N(aryl)_2$, C_3-C_7-cycloalkyl, C_1-C_6 alkyl, either unsubstituted or substituted with 1) C_3-C_7 cycloalkyl, 2) polyfluoro, or 3) two aryl groups, and

X is a single bond.

Exemplifying this class are the following compounds:

(1) 5-Amino-3-butyl-4-[(2'-carboxybiphen-4-yl)-methyl]-1-phenylpyrazole;
(2) 5-Amino-3-butyl-1-phenyl-4-[(2'-(tetrazol-5-yl)-biphen040yl)methyl]pyrazole;
(3) 3-Butyl-5-hydroxy-1-phenyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;
(4) 3-Butyl-5-carboxy-1-phenyl-4-'[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;
(5) 3-Butyl-5-carbomethoxy-1-phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;
(6) 3-Butyl-5-hydroxymethyl-1-phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;
(7) 3-Butyl-1-(2-chloro)phenyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-5-hydroxymethyl-pyrazole;
(8) 1-(2-Chloro)phenyl-5-hydroxymethyl-3-propyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;
(9) 3-Butyl-5-carboxy-1-(2-chloro)phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;
(10) 3-Butyl-5-carbomethoxy-1-(2-methyl)phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;
(11) 3-Butyl-5-carbomethoxy-1-(2-nitro)phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;
(12) 3-Butyl-5-carbomethoxy-1-(2-trifluoromethyl)-phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-pyrazole;
(13) 3-Butyl-5-carbomethoxy-1-(2-chloro-4-methoxy)-phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-pyrazole;

(14) 3-Butyl-5-carbomethoxy-1-propyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(15) 3-Butyl-5-carbomethoxy-1-isobutyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(16) 3-Butyl-5-carbomethoxy-1-pentafluoroethyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(17) 3-Butyl-5-carbomethoxy-1-cyclohexylmethyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(18) 3-Butyl-5-carbomethoxy-1-dimethylaminomethyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(19) 3-Butyl-5-acetamido-1-(2-chloro)phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(20) 3-Butyl-1-(2-chloro)phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-5-trifluoromethylsulfonamidopyrazole;

(21) 3-Butyl-1-(2-chloro)phenyl-5-dimethylamino-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(22) 3-Butyl-1-(2-chloro)phenyl-5-propylamino-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(23) 3-Butyl-1-(2-chloro)phenyl-5-methoxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(24) 3-Butyl-1-(2-chloro)phenyl-5-propyloxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(25) 3-Butyl-1-(2-chloro)phenyl-5-methylsulfinyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(26) 3-Butyl-1-(2-chloro)phenyl-5-methylsulfonyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(27) 3-Butyl-1-(2-(trifluoromethyl)phenyl)-5-carboxy-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(28) 3-Butyl-1-(2-(trifluoromethyl)phenyl)-5-carbethoxy-4-[(2'-(N-cyclopropanecarbonyl)-sulfonamidobiphen-4-yl)methyl]pyrazole;

(29) 3-Butyl-1-(2-(trifluoromethyl)phenyl)-5-trifluoromethanesulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(30) 3-Butyl-1-(2-(trifluoromethyl)phenyl)-5-pentafluoromethanesulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(31) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-carboxy-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(32) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-carboethoxy-4-[(2'-(N-cyclopropanecarbonyl)-sulfonamidobiphen-4-yl)methyl]pyrazole;

(33) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-trifluoromethanesulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(34) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-pentafluoroethanesulfonamidosulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)-methyl]pyrazole;

(35) 3-Butyl-1-(2,6-dichlorophenyl)-5-carboxy-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)-methyl]pyrazole;

(36) 3-Butyl-1-(2,6-dichlorophenyl)-5-carboethoxy-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)-methyl]pyrazole;

(37) 3-Butyl-1-(2,6-dichlorophenyl)-5-trifluoromethanesulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(38) 3-Butyl-1-(2,6-dichlorophenyl)-5-pentafluoroethanesulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(39) 3-Butyl-1-(trifluoromethyl)phenyl)-5-carboxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(40) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-carboethoxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(41) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-trifluoromethanesulfonamido-4-[(2'-(N-butyryl)-sulfonamidobiphen-4-yl)methyl]-pyrazole;

(42) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-pentafluoroethanesulfonamido-4-[(2'-(N-butyryl)-sulfonamidobiphen-4-yl)methyl]-pyrazole;

(43) 3-Propyl-1-(2-(trifluoromethyl)phenyl-5-carboxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(44) 3-Propyl-1-(2-(trifluoromethyl)phenyl-5-carboethoxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(45) 3-Propyl-1-(2-(trifluoromethyl)phenyl-5-trifluoromethanesulfonamido-4-[(2'-(N-butyryl)-sulfonamidobiphen-4-yl)methyl]-pyrazole;

(46) 3-Propyl-1-(2-(trifluoromethyl)phenyl-5-pentafluoroethanesulfonamido-4-[(2'-(N-butyryl)-sulfonamidobiphen-4-yl)methyl]-pyrazole;

(47) 3-Butyl-1-(2,6-(dichlorophenyl)-5-carboxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(48) 3-Butyl-1-(2,6-(dichlorophenyl)-5-carboethoxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(49) 3-Butyl-1-(2,6-(dichlorophenyl)-5-trifluoromethanesulfonamido-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(50) 3-Butyl-1-(2,6-(dichlorophenyl)-5-pentafluoroethanesulfonamido-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(51) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-carboxy--4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-pyrazole;

(52) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-carboethoxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrazole;

(53) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-trifluoromethanesulfonamido-4-[(2'-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrazole;

(54) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-pentafluoroethanesulfonamido-4-[(2'-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrazole;

(55) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-carboxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrazole;

(56) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-carboethoxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrazole;

(57) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-trifluoromethanesulfonamido-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(58) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-pentafluoroethanesulfonamido-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(59) 3-Butyl-1-(2,6-dichlorophenyl)-5-carboxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(60) 3-Butyl-1-(2,6-dichlorophenyl)-5-carboethoxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(61) 3-Butyl-1-(2,6-dichlorophenyl)-5-trifluoromethanesulfonamido-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(62) 3-Butyl-1-(2,6-dichlorophenyl)-5-pentafluoroethanesulfonamido-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(63) Ethyl 3-butyl-1-(2,4-dichlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(64) 3-Butyl-1-(2,4-dichlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(65) Ethyl 3-butyl-1-(4-methoxyphenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(66) 3-Butyl-1-(4-methoxyphenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(67) Ethyl 3-butyl-1-(2-nitrophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(68) 3-Butyl-1-(2-nitrophenyl)-4-[[2'-(5-tetrazolyl)-biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(69) Ethyl 3-butyl-1-(4-methoxy-2-nitrophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(70) 3-Butyl-1-(4-methoxy-2-nitrophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(71) 3-Butyl-1-(2-pyridyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(72) 1-Benzyl-3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(73) Ethyl 1-(2-chlorophenyl)-3-propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(74) 1-(2-Chlorophenyl)-3-propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(75) 1-(2,6-Dichlorophenyl)-3-propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(76) Ethyl 3-propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylate

(77) 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylic acid

(78) Ethyl 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-(trifluoroethyl)-1H-pyrazole-5-carboxylate

(79) 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]-1-(2,2,2-(trifluoroethyl)-1H-pyrazole-5-carboxylic acid

(80) Ethyl 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(81) 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]-1H-pyrazole-5-carboxylic acid

(82) 3-Butyl-1-(2-chlorophenyl)-4-[[2'-[N-(cyclopropanecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(83) 3-Butyl-1-(2,6-dichlorophenyl)-4-[[2'-[N-isobutyrylsulfamoyl]biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(84) 3-Butyl-4-[[2'-[N-(3-cyclopentylpropionyl)sulfamoyl]biphenyl-4-yl]methyl]-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylic acid

(85) 3-Butyl-4-[[2'-[N-(diphenylacetyl)sulfamoyl]biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(86) 4-[[2'-[N-(N,N-diphenylcarbamoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-propyl-1H-pyrazole-5-carboxylic acid

(87) 4-[[2'-[N-(Diphenylacetyl)sulfamoyl]biphenyl-4-yl]methyl]-3-propyl-1H-pyrazole-5-carboxylic acid

(88) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]methyl]-1-(2-chlorophenyl)-3-propyl-1H-pyrazole-5-carboxylic acid

(89) 1-(2,6-Dichlorophenyl)-3-propyl-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(90) 3-Butyl-4-[[2'-[N-(pyrimidin-2-yl)sulfamoyl]biphenyl-4-yl]methyl]-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylic acid

(91) 4-[[2'-[N-(4-Nitrophenyl)sulfamoyl]biphenyl-4-yl]methyl]-3-propyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxylic acid

(92) 4-[[2'-[N-(Diphenylacetyl)sulfamoyl]biphenyl-4-yl]methyl]-3-ethyl-1H-pyrazole-5-carboxylic acid

(93) 3-Butyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-1-(2,6-dichlorophenyl)-1H-pyrazole-5-carboxylic acid

(94) 4-[[2'-[N-(Benzenesulfonyl)carbamoyl]biphenyl-4-yl]methyl]-3-butyl-1-(2-chlorophenyl)-1H-pyrazole-5-carboxylic acid

(95) 5-[N-(Benzenesulfonyl)carbamoyl]-3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole

(96) 3-Butyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]-methyl]-5-(trifluoromethanesulfonamido)-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole

(97) 3-Butyl-1-(2-chlorophenyl)-5-(pentafluoro-ethanesulfonamido)-4-[[2'-(tetrazol-5-yl)-biphenyl-4-yl]methyl]-1H-pyrazole

(98) 3-Butyl-5-(pentafluoroethanesulfonamido)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-1-[2-(tri-fluoromethyl)phenyl]-1H-pyrazole

(99) 4-[[2'-[N-(Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-butyl-1-[2-(chlorophenyl)-5-(tri-fluoromethanesulfonamido)-1H-pyrazole

(100) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]methyl]-3-butyl-5-(trifluoromethanesulfonamido)-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole

(101) 3-Butyl-1-(2-chlorophenyl)-4-[[2'-[N-(cyclopro-panecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-1H-pyrazole

(102) 3-Butyl-1-(2-chlorophenyl)-4-[[2'-[N-(cyclopro-panecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-(pentafluoroethanesulfonamido)-1H-pyrazole

(103) 3-Butyl-4-[[2'-[N-(cyclopropanecarbonyl)sulfamo-yl]biphenyl-4-yl]methyl]-5-(trifluoromethane-sulfonamido)-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole

(104) 1-(2-Chlorophenyl)-3-propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-1H-pyrazole

(105) 3-Propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]-methyl]-5-(trifluoromethanesulfonamido)-1-[2-(trifluoromethyl)phenyl-1H-pyrazole

(106) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-1-(2-chlorophenyl)-3-propyl-5-(trifluoromethanesulfonamido)-1H-pyrazole

(107) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-propyl-5-(trifluoromethanesulfonamido)-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole

(108) 1-(2-Chlorophenyl)-4-[[2'-[N-(cyclopropanecarbonyl)sulfamonyl]biphenyl-4-yl]methyl]-3-propyl-5-(trifluoromethanesulfonamido)-1H-pyrazole

(109) 4-[[2'-[N-(Cyclopropanecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-3-propyl-5-(trifluoromethanesulfonamido)-1-[2-(trifluoromethyl)-phenyl]-1H-pyrazole

(110) 1-(2-Chlorophenyl)-4-[[2'-[N-(cyclopropanecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-(pentafluoroethanesulfonamido)-3-propyl-1H-pyrazole

(111) 1-(2-Chlorophenyl)-5-(pentafluoroethanesulfonamido)-3-propyl-4-[[2'-(tetrazol-5-yl)-biphenyl-4-yl]methyl]-1H-pyrazole

(112) 3-Butyl-1-(2-chlorophenyl)-5-(trifluoromethanesulfonamido)-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]-1H-pyrazole.

(113) 3-Butyl-5-[N-(isopropylsulfonyl)carbamoyl]-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoromethyl)-1H-pyrazole

(114) 3-Butyl-5-[N-(cyclopropanesulfonyl)carbamoyl]-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoromethyl)-1H-pyrazole

(115) 3-Butyl-5-(4-fluorobenzenesulfonamide)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoromethyl)-1H-pyrazole

(116) 3-Butyl-5-(3-pyridinesulfonamide)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoromethyl)-1H-pyrazole

Several methods for preparing the compounds of this invention are illustrated in the ensuing Schemes.

ABBREVIATIONS USED IN SCHEMES AND EXAMPLES

Reagents:

NBS	N-bromosuccinimide
AIBN	2,2'-azobis(isobutyronitrile)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Ac_2O	acetic anhydride
TEA or Et_3N	triethylamine
DMAP	4-dimethylaminopyridine
PPh_3	triphenylphosphine
TFA	trifluoroacetic acid
TMS-Cl	trimethylsilyl chloride
Im	imidazole
AcSK	potassium thioacetate
p-TsOH	p-toluenesulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

Solvents:

DMF	dimethylformamide
HOAc (AcOH)	acetic acid
EtOAc (EtAc)	ethyl acetate
Hex	hexane
THF	tetrahydrofuran
DMSO	dimethylsulfoxide
MeOH	methanol
iPrOH	isopropanol
EtOH	ethanol

Others:

rt	room temperature
TBDMS	t-butyldimethylsilyl
OTf	OSO_2CF_3
OTs	OSO_2-(4-methyl)phenyl
OMs	OSO_2CH_3
Ph	phenyl
FAB-MS (FABMS)	Fast atom bombardment mass spectroscopy
NOE	Nuclear Overhauser Effect
SiO_2	silica gel
trityl	triphenylmethyl
LG	leaving group
TLC	thin layer chromatography
MPLC	medium pressure liquid chromatography
MPM	(4-methoxyphenyl)methyl

Pyrazoles substituted in the 1,3,4,5-positions and isothiazoles substituted in the 3,4,5-positions may be prepared as shown in Schemes 1 through 6.

Scheme 1 shows how the dianion of ethyl hydrogen malonate can be acylated with an R^6 acyl chloride then acidified to give the α-unsubstituted-ß-ketoester shown.[1] The ß-ketoester is then alkylated with sidechain 1 using sodium hydride in DMSO (or other suitable base in a suitable solvent) to give α-substituted-ß-ketoester 2. Condensation of the ß-ketoester 2 with an R^7 hydrazine as shown in Scheme 2 results in the formation of pyrazole 3. Similarly, condensation of β-ketoester 2 with hydroxylamine as shown in Scheme 3 results in the formation of isoxazole 4.

Scheme 4 provides a route to the useful intermediate β-ketonitrile 5. Cyanoacetic acid can be condensed with an R^6 acyl chloride to give the R^6 α-unsubstituted-β-ketonitrile.[2] This can then be α-alkylated using NaH in DMSO (or other suitable base and solvent) and the appropriate sidechain electrophile to afford 5. Ketonitrile 5 will afford 5-aminopyrazole 6 when condensed with an R^7 hydrazine (Scheme 5). Likewise, 5-aminoisoxazole 7 results from the condensation of ketonitrile 5 with hydroxylamine (Scheme 6).

One example of the assembly of an isothiazole is shown in Schemes 7, 8, and 9. Lithium acetylide displacement of the leaving group of compound 1 would give intermediate 8. This material

can be deprotonated with butyllithium, LDA, or other suitable base and added to ethyl chloroformate to give the ethyl propiolate derivative 9. Scheme 8 provides a route to the precursor of the unstable nitrile N-sulfide. Condensation of an R^6 amide with chlorocarbonylsulfenyl chloride will give the oxathiazolone 11. Heating this material in the presence of the substituted propiolic ester 9 will give a mixture of [3+2]-dipolar cycloaddition products which may then be separated.[3]

Scheme 10 gives an alternate preparation of an isoxazole via [3+2]-dipolar cycloaddition. Deprotonation of intermediate 8 as before followed by addition of formaldehyde and subsequent protection (illustrated here with the methoxyphenylmethyl (MPM) group) will give substituted propargyl alcohol 13. Alternatively, 13 could be prepared from 1 and the anion of O-protected propargyl alcohol, or from the reduction and protection of the propiolate ester 9. Addition of an R^6 nitrile oxide to the alkyne 13 will give a mixture of products with one component being isoxazole 14. Separation of isomers followed by Raney Nickel reduction and intoduction of the sulfur using P_2S_5 with or without an oxidant will give the corresponding isothiazole 15.[4] The latent alcohol may be deprotected with DDQ.[5] Oxidation would give the corresponding carboxylic acid. Alternatively, the R^6 nitrile oxide could be added directly to the propiolate ester 9.

The ß-ketonitrile 5 can be converted to the ß-amino-α,ß-unsaturated nitrile 16 upon treatment of 5 with concentrated ammonium hydroxide (Scheme 11).

Alternatively, the ß-enol triflate[6] or phosphate[7] could be treated with ammonia to give 16. Conversion of this material to the 5-aminoisothiazole 17 could be achieved using the methods described by Adams and Slack.[8] The 5-aminoisothiazole 17 can be a final product (after any required deprotection) or may be used as an intermediate to the carboxy derivative 18. Diazotization of 17 and conversion to the bromide followed by heating with CuCN and hydrolysis would give the carboxy derivative 18. Diazotization of 17 followed by reduction with hypophosphorous acid would give the 5-hydridoisothiazole.[9]

Scheme 12 provides a route for the preparation of acyl sulfonamides 20. The carboxylic acid can be activated by conversion to the acid chloride by various methods including treatment with refluxing thionyl chloride or preferably with oxalyl chloride and a catalytic amount of DMF at low temperature.[10] Activation by conversion to the acyl imidazole can be achieved upon treatment of acid 19 with carbonyldiimidazole. N,N-Diphenylcarbamoyl anhydride intermediates may be prepared as activated carbonyls.[11] Treatment of the activated carbonyls with alkali metal salts of alkyl or aryl sulfonamides or with the sulfonamide and DBU will give the expected acyl sulfonamide 20.[12]

Scheme 13 provides a route to the isomeric acyl sulfonamides 28. The commerically available bromobenzenesulfonyl chloride 21 may be converted to the corresponding sulfonamide upon treatment with ammonia or ammonium carbonate. Protection with the triphenylmethyl group gives sulfonamide 23. Palladium

catalyzed cross-coupling of 23 with the aryltrimethyltin derivative 24 gives the biaryl 25.[13] Treatment of this material with N-bromosuccinimide and catalytic AIBN in refluxing CCl_4 will give the alkylating agent 26. The bromide 26 may now be used as the alkylating agent 1 shown in previous schemes to give intermediate 27. Deprotection and acylation will give the acyl sulfonamide 28.

A useful pathway for the synthesis of compounds of Formula I wherein $K=NR^7$ and $R^8=CO_2H$ or CO_2R^4 is illustrated in Scheme 14. In this case, the side chain attached to C^4 of the pyrazole ring is [2'-(5-tetrazolyl)biphenyl-4-yl]methyl. Reaction of the appropriate methyl ketone 29 with diethyl oxalate (30) in the presence of sodium ethoxide yields the 2,4-diketo ester 31.[14] Treatment of 31 with methoxyamine hydrochloride in the presence of 3A molecular sieves (method based on that of Mukaiyama, et al.[15]) selectively gives the 2-methoxime derivative 32. Reaction of 32 with 4-bromomethyl-2'-cyanobiphenyl (33)[16] affords the desired alkylated product 34. When 34 is heated with the appropriate hydrazine hydrochloride 35, preferably at about 100-110°C in acetic acid, optionally containing a cosolvent such as 2-methoxyethanol, the pyrazolecarboxylate 36 is formed. This ring formation is highly regioselective in the case of arylhydrazine hydrochlorides and at least certain alkylhydrazine hydrochlorides. The cyano group of 36 is next converted to the tetrazole 37 upon heating with trimethyltin azide in toluene[17], the free

tetrazole being obtained upon treatment with silica gel. Saponification of 37, typically by warming in a mixture of aqueous sodium hydroxide and methanol followed by acidification, provides the pyrazolecarboxylic acid 38. The isoxazole analog of 38 (K=O in Formula I) may be prepared analogously by substituting hydroxylamine hydrochloride for 35 in Scheme 14.

A similar sequence to pyrazolecarboxylates in which the tetrazole group of 37 or 38 is replaced by acylsulfonamide is shown in Scheme 15. Alkylation of 32 (from Scheme 14) with the t-butyl sulfonamide intermediate 39 (see Scheme 17) yields 40, which reacts with the hydrazine salt 35 to give the pyrazole 41. The free sulfonamide 42 is obtained by deprotection of 41 with trifluoroacetic acid in the presence of anisole. Acylation of the sulfonamide, for example, with an acid chloride 43 in pyridine (see also Scheme 13), yields the acylsulfonamide 44, which may then be saponified to 45. Alternative acylation conditions may be employed. The use of an N-acylimidazole derivative (generated from the acid with 1,1'-carbonyldiimidazole) in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in THF is also an effective method. In some cases the acid chloride in Scheme 15 may be replaced by an acid anhydride, as in the case of trifluoroacetic anhydride. It should be noted that for 44 (R^{23}=CF_3), the trifluoroacetylsulfonamide may be hydrolyzed during the saponification step, in which case reacylation at the free acid stage yields 45 (R^{23}=CF_3).

Scheme 16 also shows a similar route leading to pyrazolecarboxylates in which the tetrazole group of 37 or 38 is replaced by trifluoromethanesulfonamide. Alkylation of 32 (from Scheme 14) with the nitrobiphenyl species 46 (see Scheme 17) gives 47, which is carried on to the pyrazole derivative 48. Hydrogenation of the nitro group of 48 in the presence of a catalyst such as platinum oxide yields the amine 49. Treatment of 49 with trifluoromethanesulfonyl chloride or trifluoromethanesulfonic anhydride gives, depending on the conditions, either the mono(trifluoromethanesulfonyl) derivative 50 or the bis(trifluoromethanesulfonyl) derivative 51 as the major or exclusive product. The sulfonylation may be carried out in pyridine or, alternatively, in methylene chloride in the presence of a base such as 2,6-di-t-butyl-4-methylpyridine. Under the saponification conditions, both 50 and 51 are converted to the target pyrazolecarboxylic acid 52.

The synthesis of the intermediate alkylating agents 39 (see Scheme 15) and 46 (see Scheme 16) are shown in Scheme 17. Reaction of 2-bromobenzenesulfonyl chloride (21) with an excess of t-butylamine yields the *t*-butylsulfonamide 53. The trimethylstannyl derivative 24 is prepared from *p*-tolylmagnesium bromide (54) by treatment with trimethyltin chloride at -35°C to room temperature. Cross-coupling of 24 with 53 catalyzed by bis(triphenylphosphine)palladium(II) chloride in DMF at about 90°C affords the biphenyl derivative 55.

The bromomethyl species 39 is obtained by heating 55 with N-bromosuccinimide (NBS) in carbon tetrachloride in the presence of an initiator such as 2,2'-azobis(isobutyronitrile) (AIBN). Similarly, palladium(II)-catalyzed cross-coupling of 24 with 2-bromonitrobenzene (56) yields the biphenyl product 57, which is brominated as above to give 46.

Schemes 18-21 illustrate transformations of the R^8 group. Scheme 18, for example, shows the synthesis of a trifluoromethanesulfonamido group at R^8. In this illustration, compound 58 is a compound of formula I wherein R^8 is NH_2 and R^1 is tetrazol-5-yl. Reaction of 58 with trityl chloride in the presence of triethylamine gives the trityl-protected tetrazole derivative 59. Treatment of 59 with trifluoromethanesulfonic anhydride in the presence of 2,4,6-collidine provides the sulfonamide 60. Finally, 60 is deprotected with methanolic HCl (or, alternatively, with aqueous acetic acid) to give 61. Other R^8 polyfluoroalkanesulfonamides, as well as aryl or heteroaryl sulfonamides and the like, may be prepared in similar fashion. It is often convenient to use a sulfonyl chloride as the sulfonylating reagent, especially in the presence of DMAP and triethylamine. The scheme can also be modified for R^1 groups other then tetrazole, with use of suitable protection and deprotection as necessary.

In Scheme 19, 62 (a compound of formula I wherein R^8 is CO_2H) undergoes initial treatment with carbonyldiimidazole (CDI) to give an N-acylimidazole intermediate which, without isolution, is reacted with a sulfonamide in the presence of DBU to give the

acylsulfonamide of type 63 (wherein R is aryl, heteroaryl, alkyl, or perfluoroalkyl). As in Scheme 18, it may be necessary to protect the R^1 group prior to these reactions and to deprotect it afterwards.

Scheme 20 shows a route to a reversed acylsulfonamide grouping at R^8. Compound 64 (a compound of formula I wherein R^8 is NH_2) may be diazotized either under aqueous conditions with nitrous acid or under nonaqueous conditions with an alkyl nitrite such as t-butyl nitrite[18] and reacted in situ with sulfur dioxide in the presence of cupric chloride in acetic acid to give the sulfonyl chloride 65. Treatment of 65 with ammonia yields the sulfonamide 66, which can be acylated with an acid chloride in pyridine or an acylimidazole derivative in the presence of DBU. The product thus obtained is the acylsulfonamide of structure 67, wherein R is aryl, heteroaryl, alkyl, or perfluoroalkyl. The earlier comments about protection and deprotection of R^1 also apply.

The synthesis of some other sulfur-linked side chains at R^8 is shown in Scheme 21. The amino heterocycle 64 is converted to the chloro heterocycle 68 by use of nitrosyl chloride in chloroform[18]. Compound 68 is heated with a thiol in the presence of a base, such as potassium carbonate, N,N-diisopropylethylamine, or DBU, to give the thioether 69. Alternatively, 69 may be obtained directly from 64 by nonaqueous diazotization with t-butyl nitrite in the presence of a disulfide. Compound 69 can then be oxidized to either the sulfoxide 70 or the sulfone 71 using a reagent such as 30% hydrogen peroxide

(aqueous) in acetic acid or an organic peracid. The choice of reagent, stoichiometry, temperature, and reaction time govern whether 70 or 71 is the major or exclusive product. In this scheme R is alkyl, aryl, or aralkyl.

A route to a carbamoylphosphinic acid R^1 group is illustrated in the pyrazolecarboxylic acid series in Scheme 22. The amino intermediate 49 may be converted to the isocyanate 72 upon heating with phosgene in an inert solvent. Reaction of 72 with phenylphosphinic acid 73 in the presence of triethylamine, according to the method of Fox and Bailey[19], gives the carbamoylphosphinic acid derivative 74. Finally, saponification of the ester affords the pyrazolecarboxylic acid 75. This method may be extended to the use of ring substituted phenylphosphinic acids and may be modified for the preparation of other compounds of formula I outside the pyrazolecarboxylate series.

The incorporation of an aryl- or alkylphosphinoyl group of R^1 is illustrated in the pyrazolecarboxylic acid series in Scheme 23. The nitrobiphenyl intermediate is readily reduced to the amine 76 using either stanous chloride reduction or catalytic hydrogenation. The amine 76 upon diazotization with nitrous acid and treatment with cuprous bromide yields the bromobiphenyl derivative 77. The bromomethyl derivative 78 is obtained from 77 by standard NBS bromination conditions as described in previous schemes. Employing the methods of Scheme 14, 78 is converted to the pyrazolecarboxylate derivative 79. Next, 79 undergoes palladium-

catalyzed cross-coupling with a monoethyl arene- or alkanephosphonite 80, using the conditions of Xu,[20,21] to give the disubstituted phosphinate ester 81. The phosphonite intermediate 80 may be obtained by reaction of a Grignard reagent $R^{23}MgBr$ with diethyl chlorophosphite followed by partial hydrolysis.[21] Finally, both the carboxylate ester and the phosphinate ester[22] of 81 may be saponified by heating with sodium hydroxide in aqueous methanol to give 82. Again, this pathway can be modified for the preparation of other compounds of formula I outside the pyrazolecarboxylate series.

Although the reaction schemes described herein are reasonably general, it will be understood by those skilled in the art of organic synthesis that one or more functional groups present in a given compound of formula I may render the molecule incompatible with a particular synthetic sequence. In such a case an alternative route, an altered order of steps, or a strategy of protection and deprotection may be employed. In all cases the particular reaction conditions, including reagents, solvent, temperature, and time, should be chosen so that they are consistent with the nature of the functionality present in the molecule.

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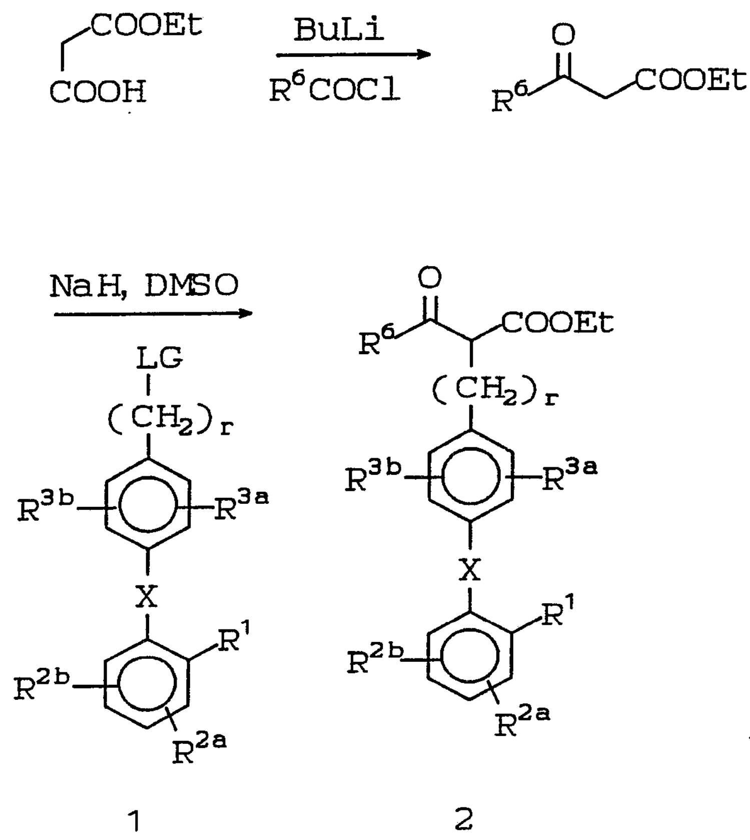
SCHEME 1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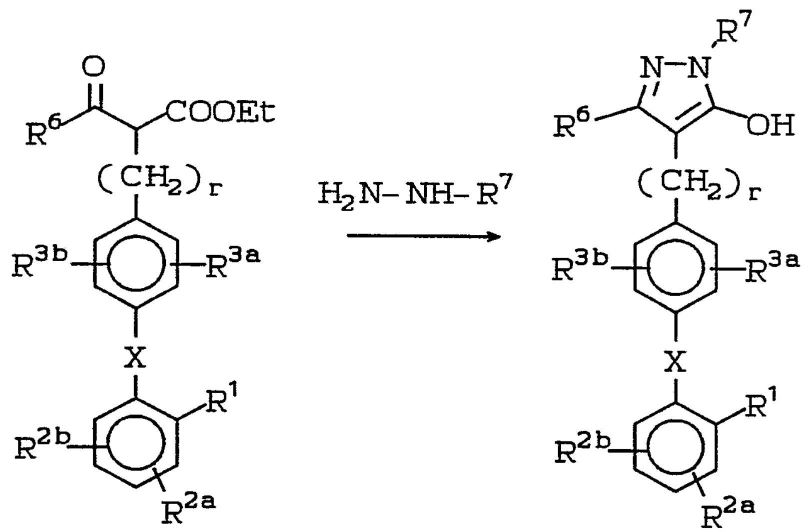
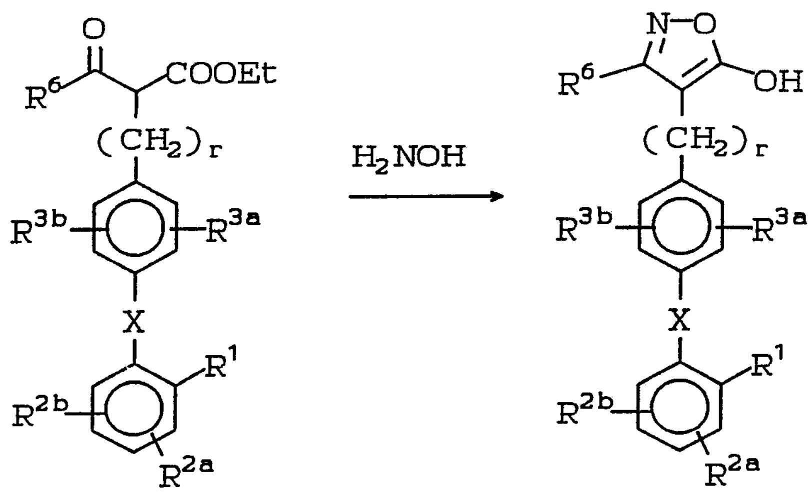
COOH
BuLi
R^6COCl
O
R^6
COOEt
NaH, DMSO
LG
$(CH_2)_r$
R^{3b}
R^{3a}
X
R^1
R^{2b}
R^{2a}
1
2

SCHEME 2



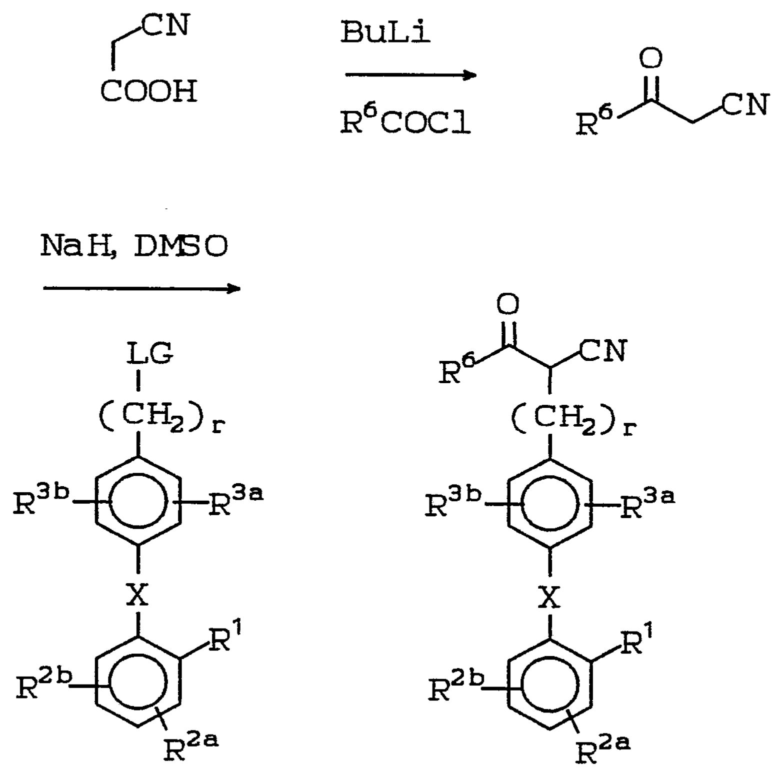
2 3

SCHEME 3



2 4

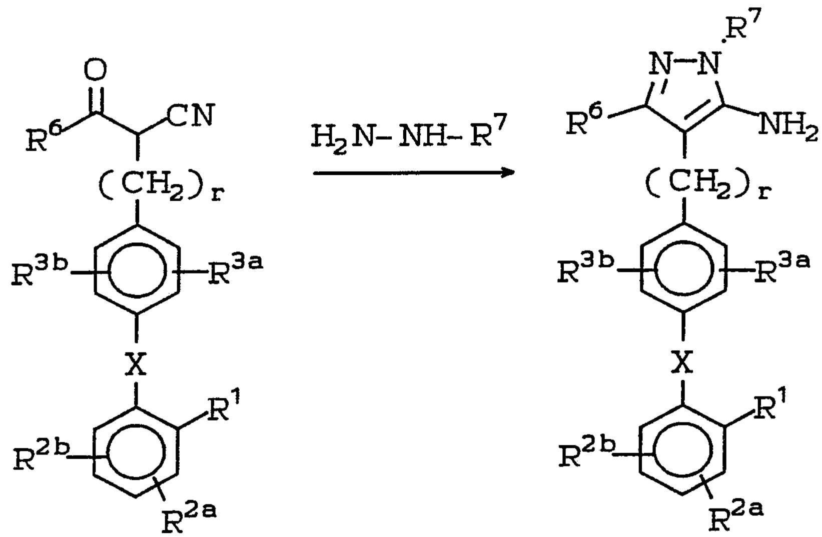
SCHEME 4


CN
COOH
BuLi
R6COCl
O
R6
CN
NaH, DMSO
LG
(CH2)r
R3b
R3a
X
R1
R2b
R2a
O
R6
CN
(CH2)r
R3b
R3a
X
R1
R2b
R2a

1

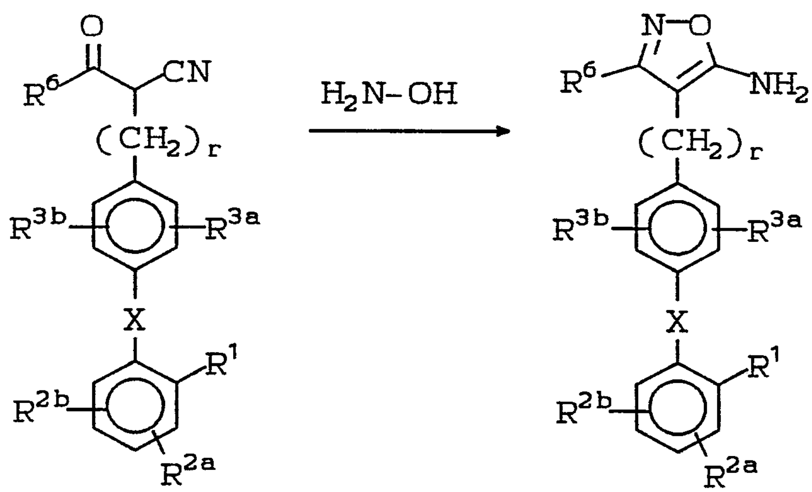
5

SCHEME 5


O
CN
R^6
$(CH_2)_r$
R^{3b}
R^{3a}
X
R^1
R^{2b}
R^{2a}
$H_2N-NH-R^7$
R^7
N–N
R^6
NH_2
$(CH_2)_r$
R^{3b}
R^{3a}
X
R^1
R^{2b}
R^{2a}

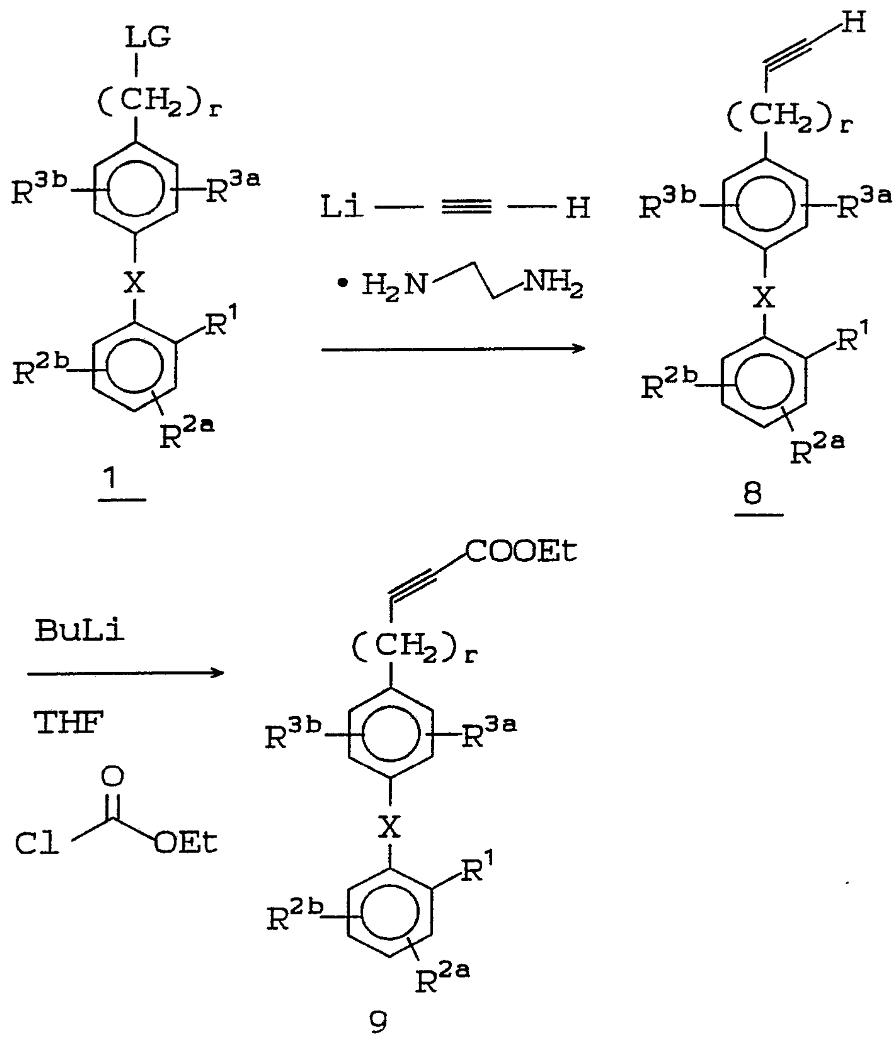
5 6

SCHEME 6

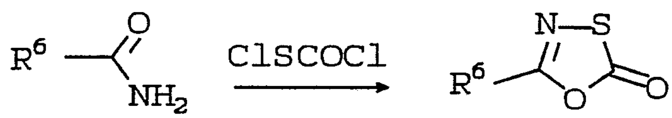

O
R6
CN
(CH2)r
R3b
R3a
X
R1
R2b
R2a
H2N-OH
N-O
R6
NH2
(CH2)r
R3b
R3a
X
R1
R2b
R2a

5 7

SCHEME 7

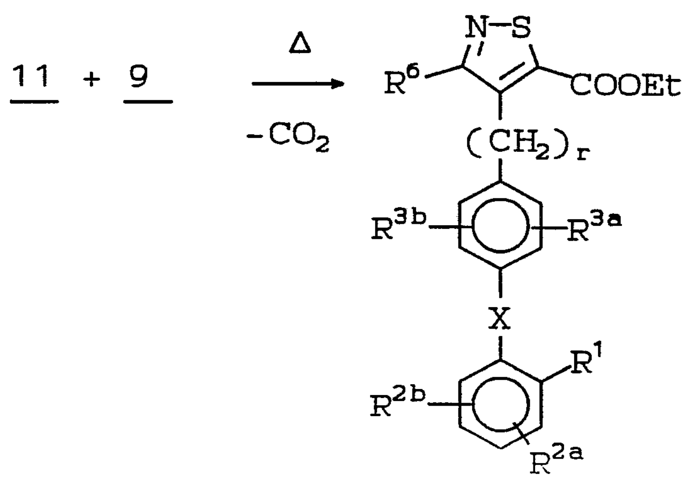

LG
(CH2)r
R3b
R3a
X
R1
R2b
R2a
1
Li — ≡ — H
• H2N NH2
H
8
BuLi
THF
O
Cl OEt
COOEt
9

SCHEME 8



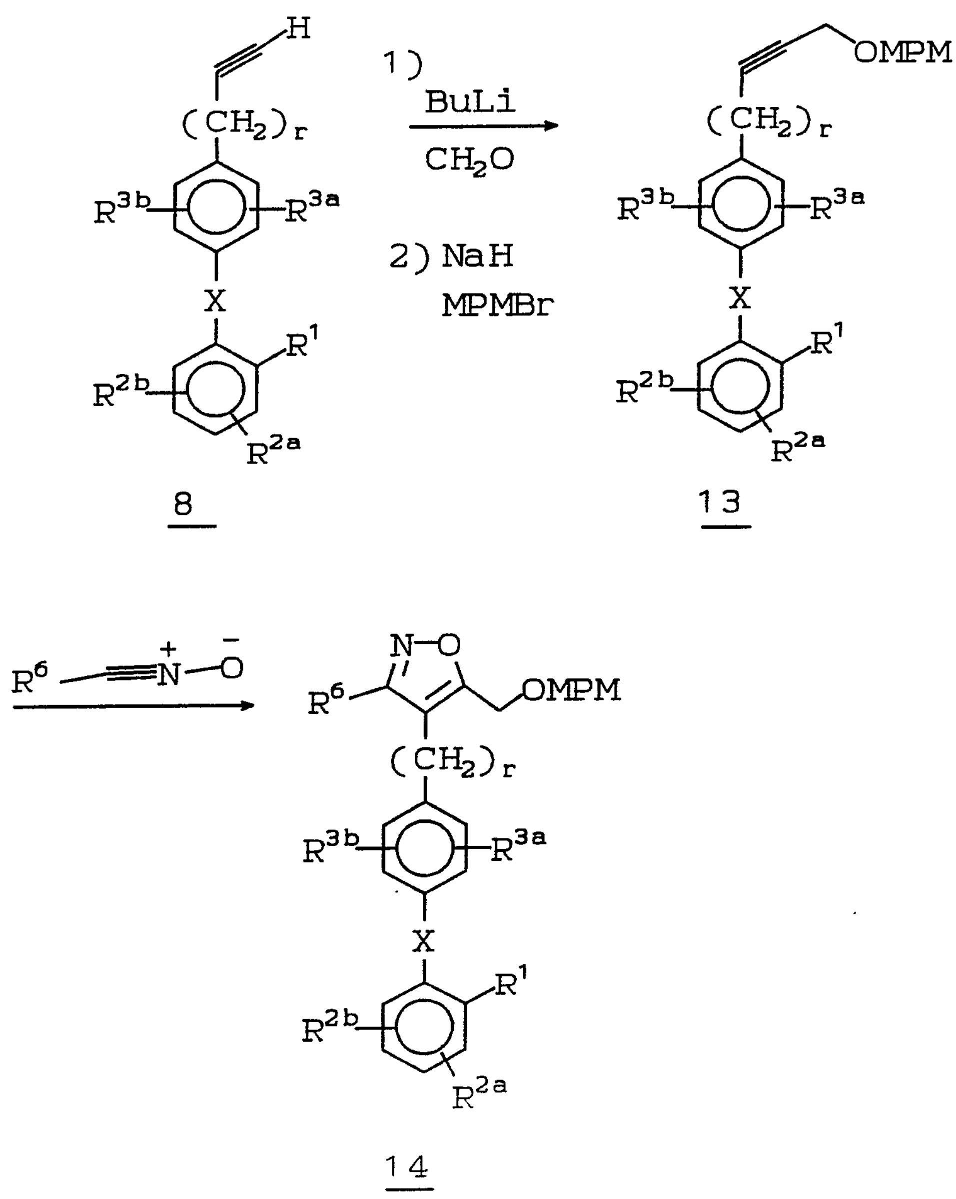
10 11

SCHEME 9



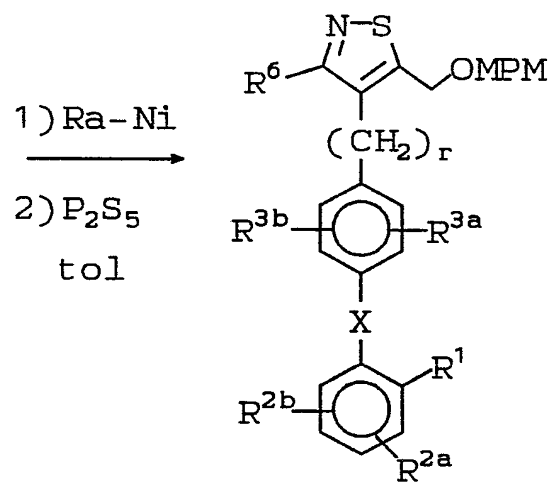
12

SCHEME 10


H
1)
BuLi
CH_2O
2) NaH
MPMBr
OMPM
$(CH_2)_r$
R^{3b}
R^{3a}
X
R^1
R^{2b}
R^{2a}
8
13
R^6
N
O
OMPM
14

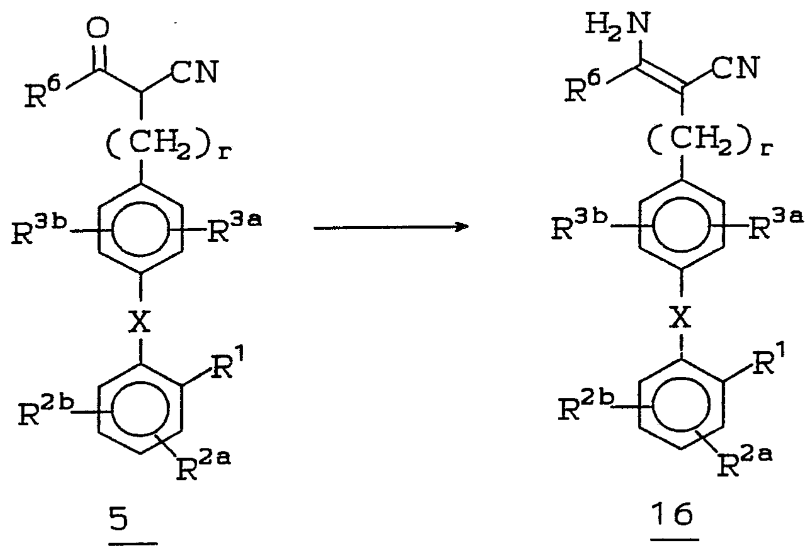
SCHEME 10 (Cont'd)

14



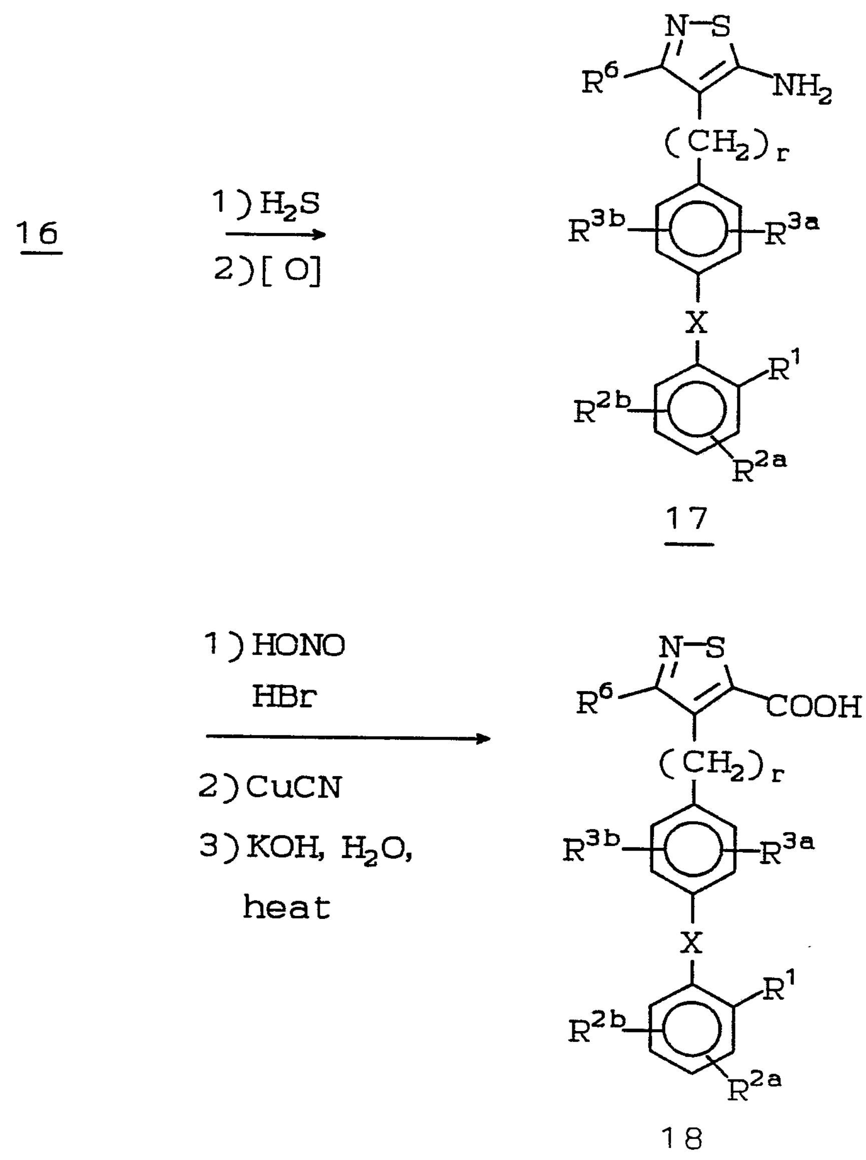
15

SCHEME 11

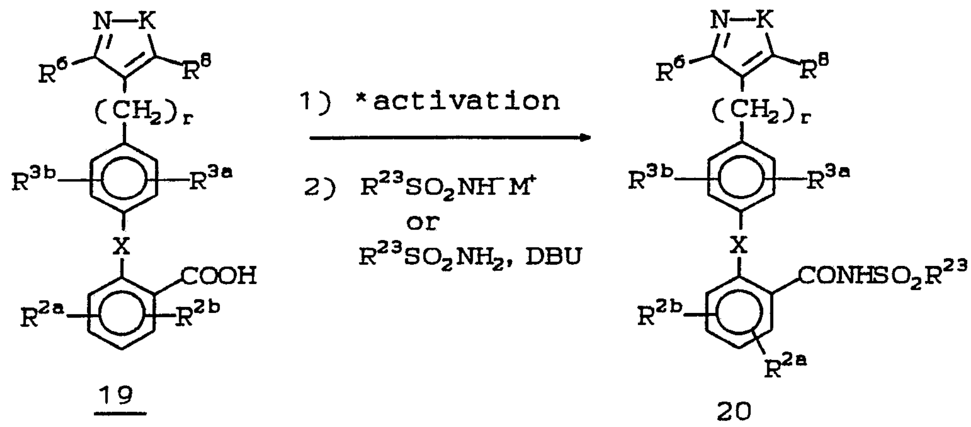


O
R6
CN
(CH2)r
R3b
R3a
X
R1
R2b
R2a
5
H2N
R6
CN
(CH2)r
R3b
R3a
X
R1
R2b
R2a
16

SCHEME 11 (CONT'D)



SCHEME 12

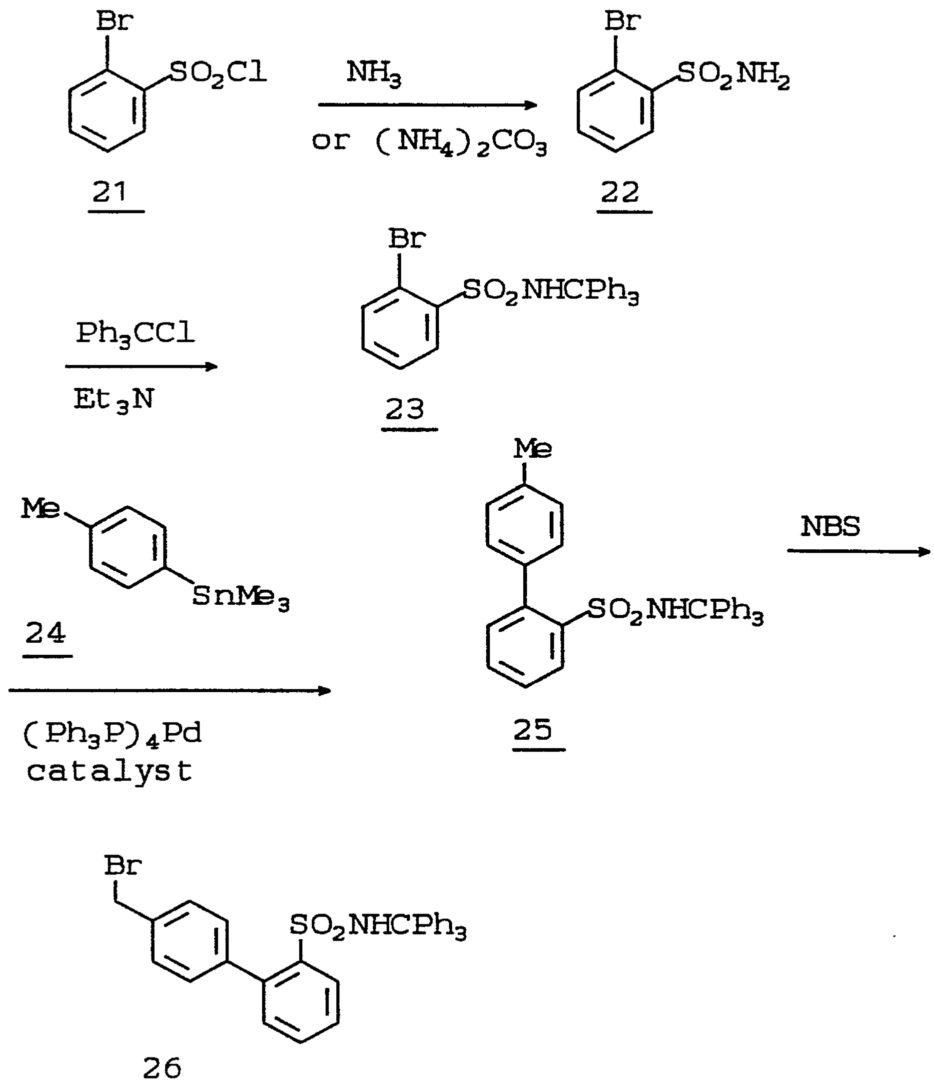


M is Na or Li

* Activation of the carboxylic acid can include:

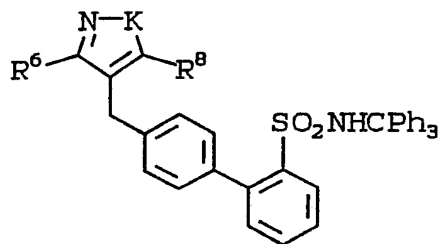
1) $SOCl_2$, Δ
2) carbonyldiimidazole
3) $(COCl)_2$, Δ
4) N(N,N-diphenylcarbamoyl)pyridinium chloride/aq. NaOH.

SCHEME 13


Br
SO_2Cl
NH_3
or $(NH_4)_2CO_3$
21
Br
SO_2NH_2
22
Ph_3CCl
Et_3N
Br
SO_2NHCPh_3
23
Me
$SnMe_3$
24
$(Ph_3P)_4Pd$
catalyst
Me
SO_2NHCPh_3
25
NBS
Br
SO_2NHCPh_3
26

SCHEME 13 (CONT.)

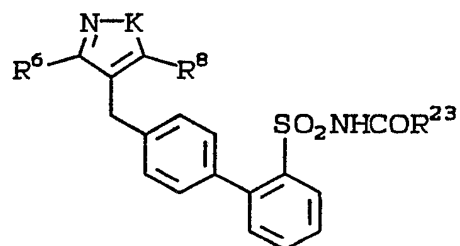
26 →



27

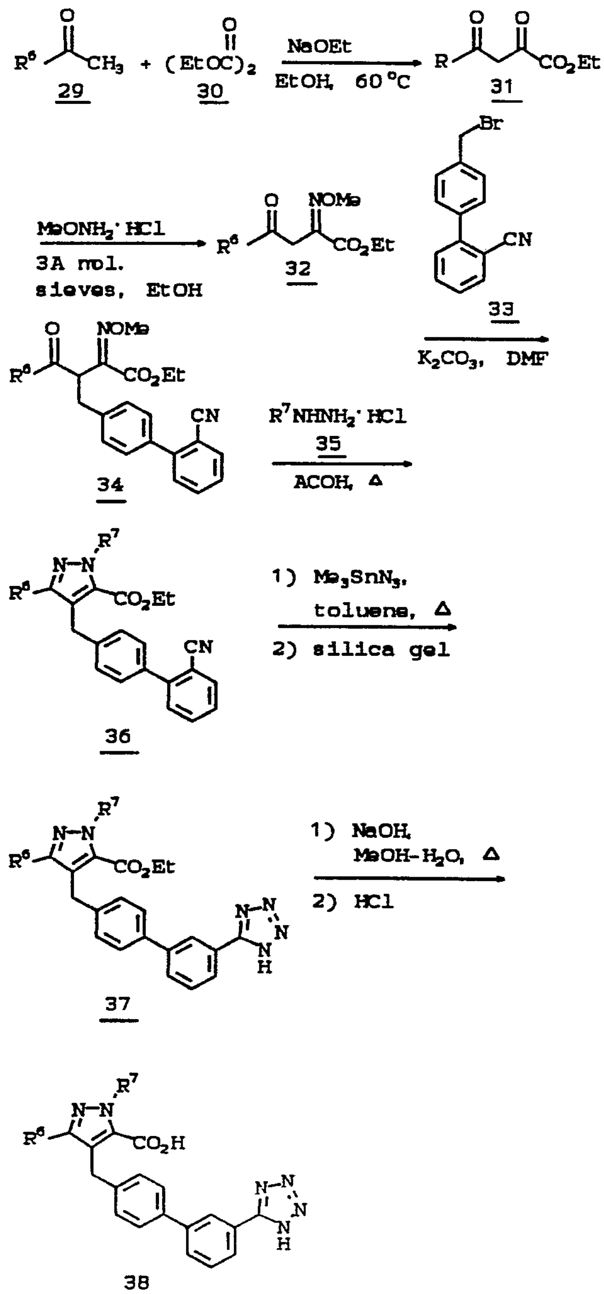
1) $AcOH/H_2O$

2) $R^{23}COCl$ or
$R^{23}CO$-imidazole or
other acylating agent

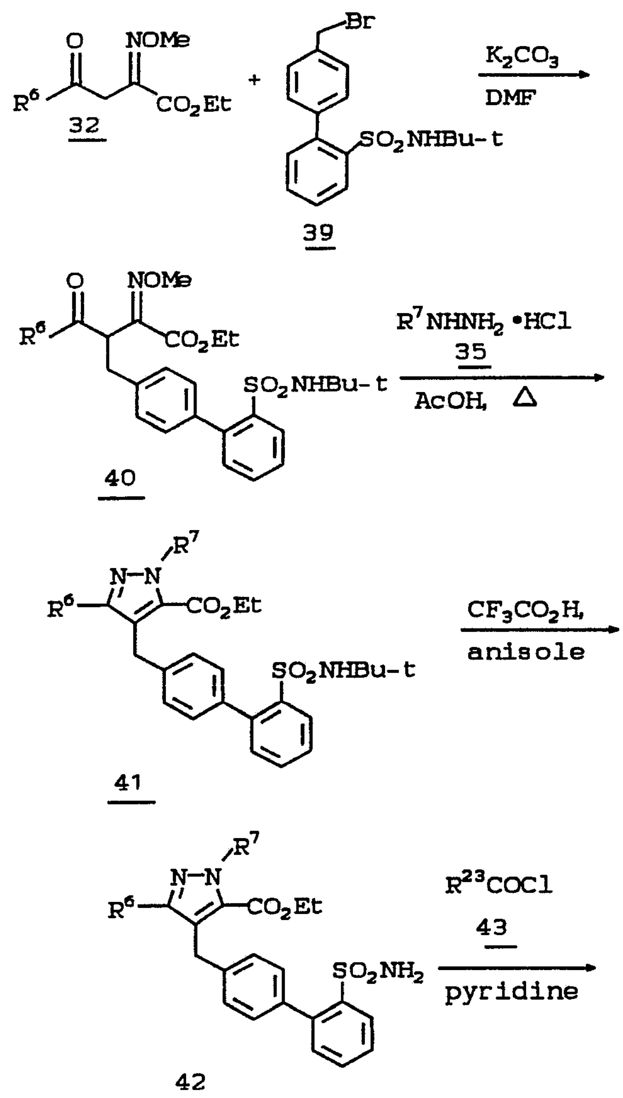


28

SCHEME 14

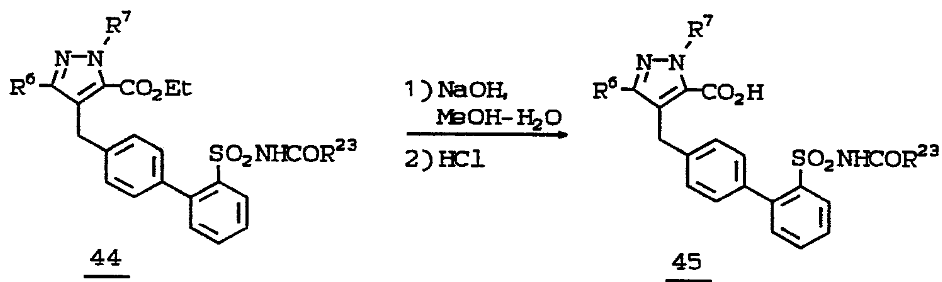

NaOEt
EtOH, 60 °C
29
30
31
$MeONH_2 \cdot HCl$
3A mol. sieves, EtOH
32
33
K_2CO_3, DMF
34
$R^7NHNH_2 \cdot HCl$
35
ACOH, Δ
36
1) Me_3SnN_3, toluene, Δ
2) silica gel
37
1) NaOH, $MeOH-H_2O$, Δ
2) HCl
38

SCHEME 15

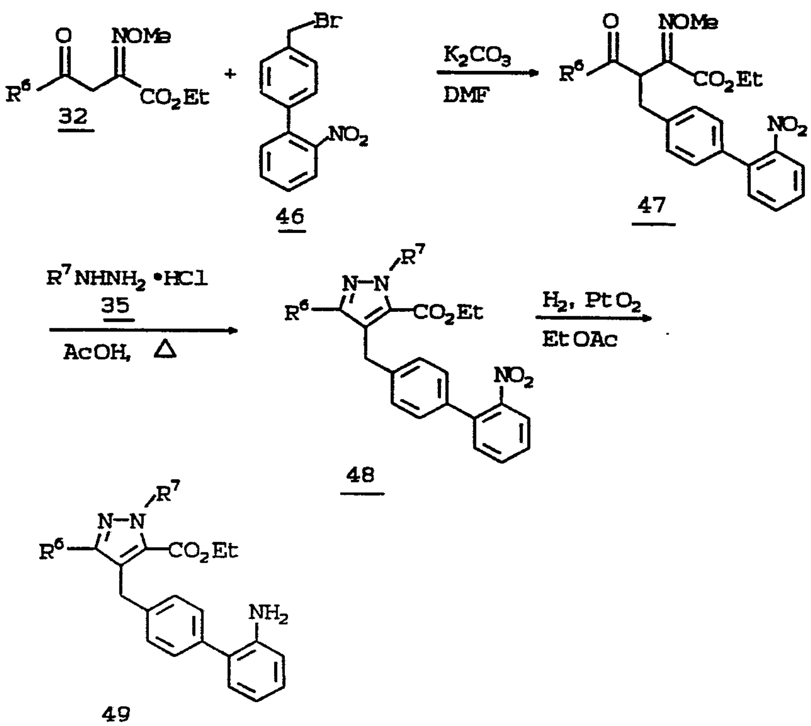


R^6
O
NOMe
CO_2Et
32
+
Br
SO_2NHBu-t
39
K_2CO_3
DMF
O
NOMe
R^6
CO_2Et
SO_2NHBu-t
40
$R^7NHNH_2 \cdot HCl$
35
AcOH, Δ
R^7
N—N
R^6
CO_2Et
SO_2NHBu-t
41
CF_3CO_2H,
anisole
R^7
N—N
R^6
CO_2Et
SO_2NH_2
42
$R^{23}COCl$
43
pyridine

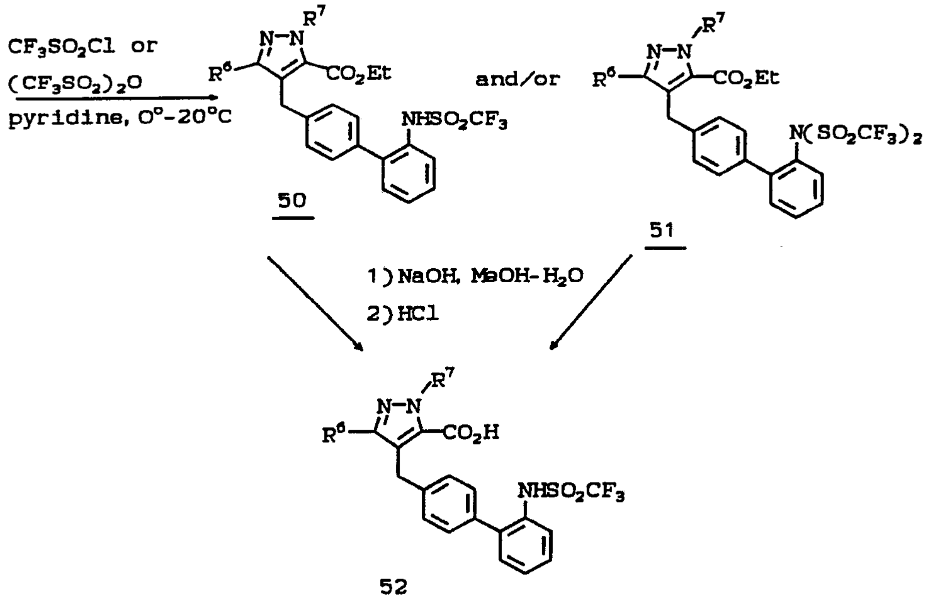
SCHEME 15 CONT'D



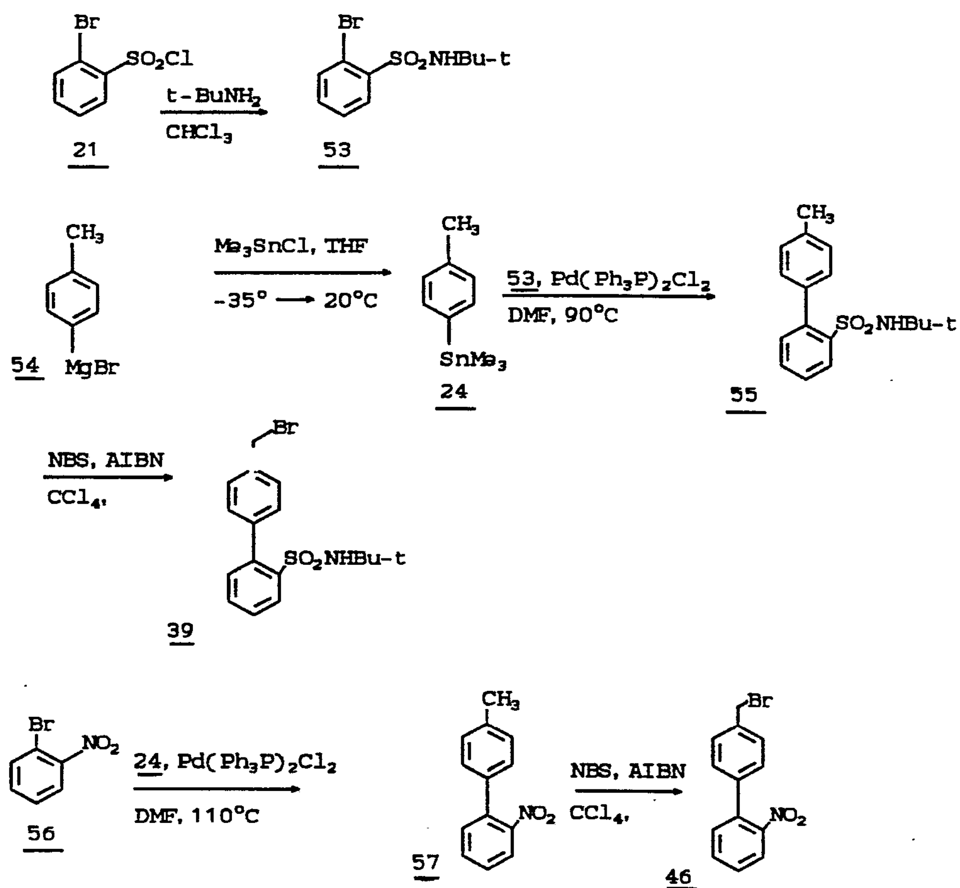
SCHEME 16



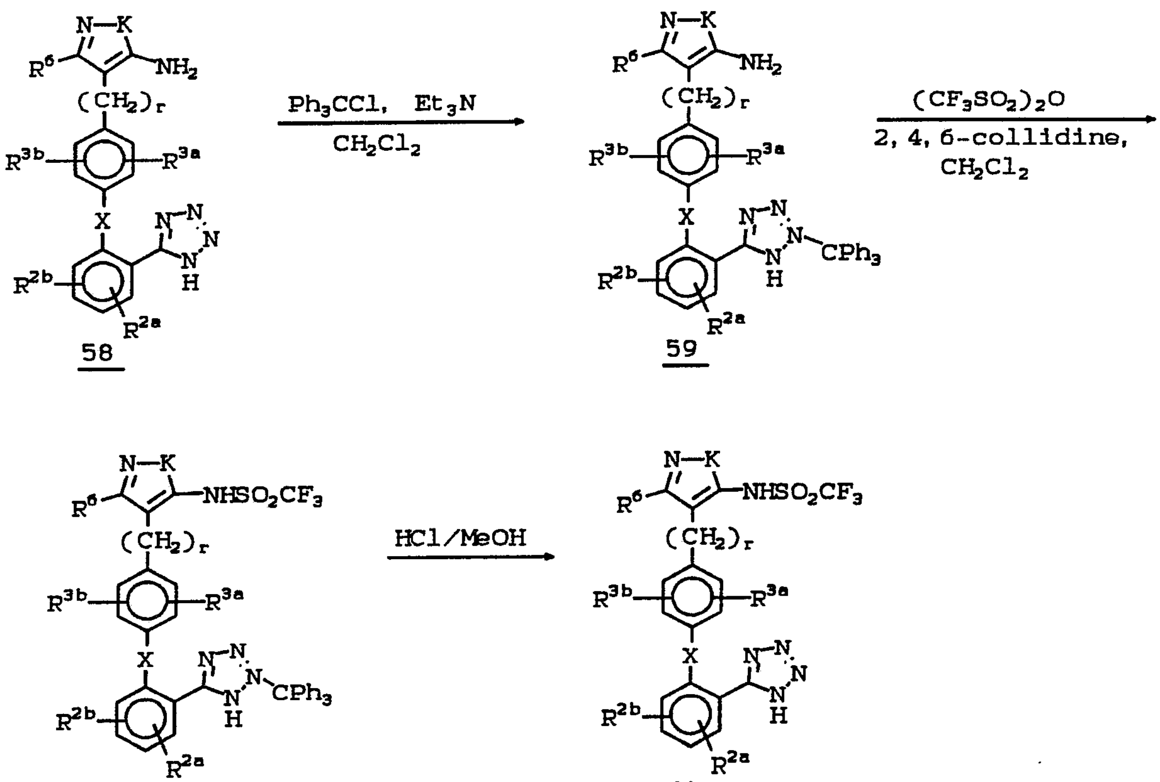
SCHEME 16 CONT'D



SCHEME 17



SCHEME 18



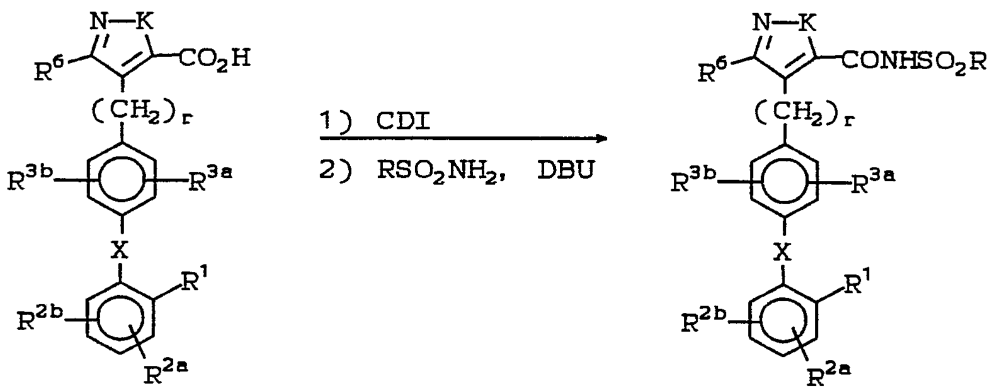
58

59

60

61

SCHEME 19

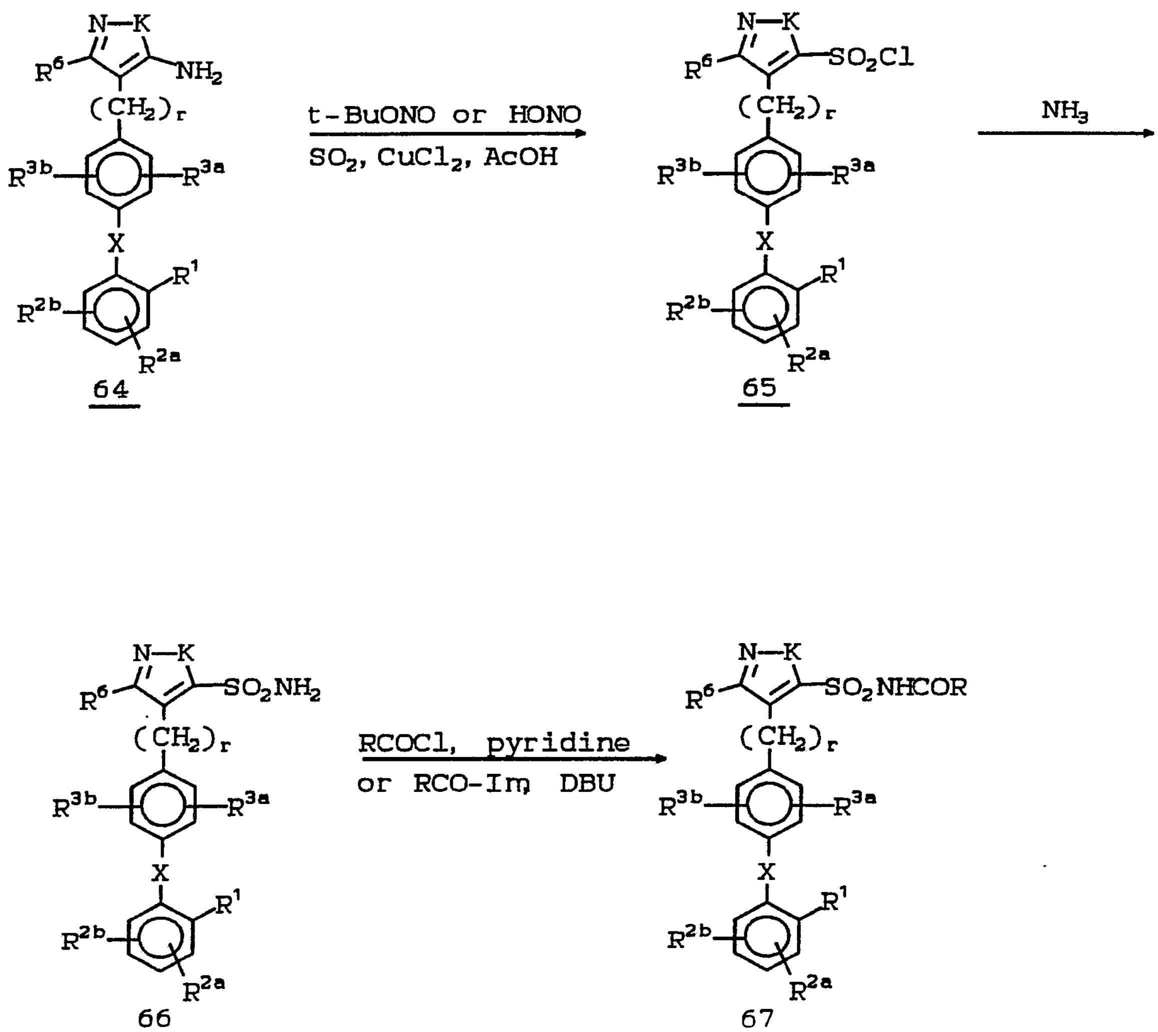


62

63

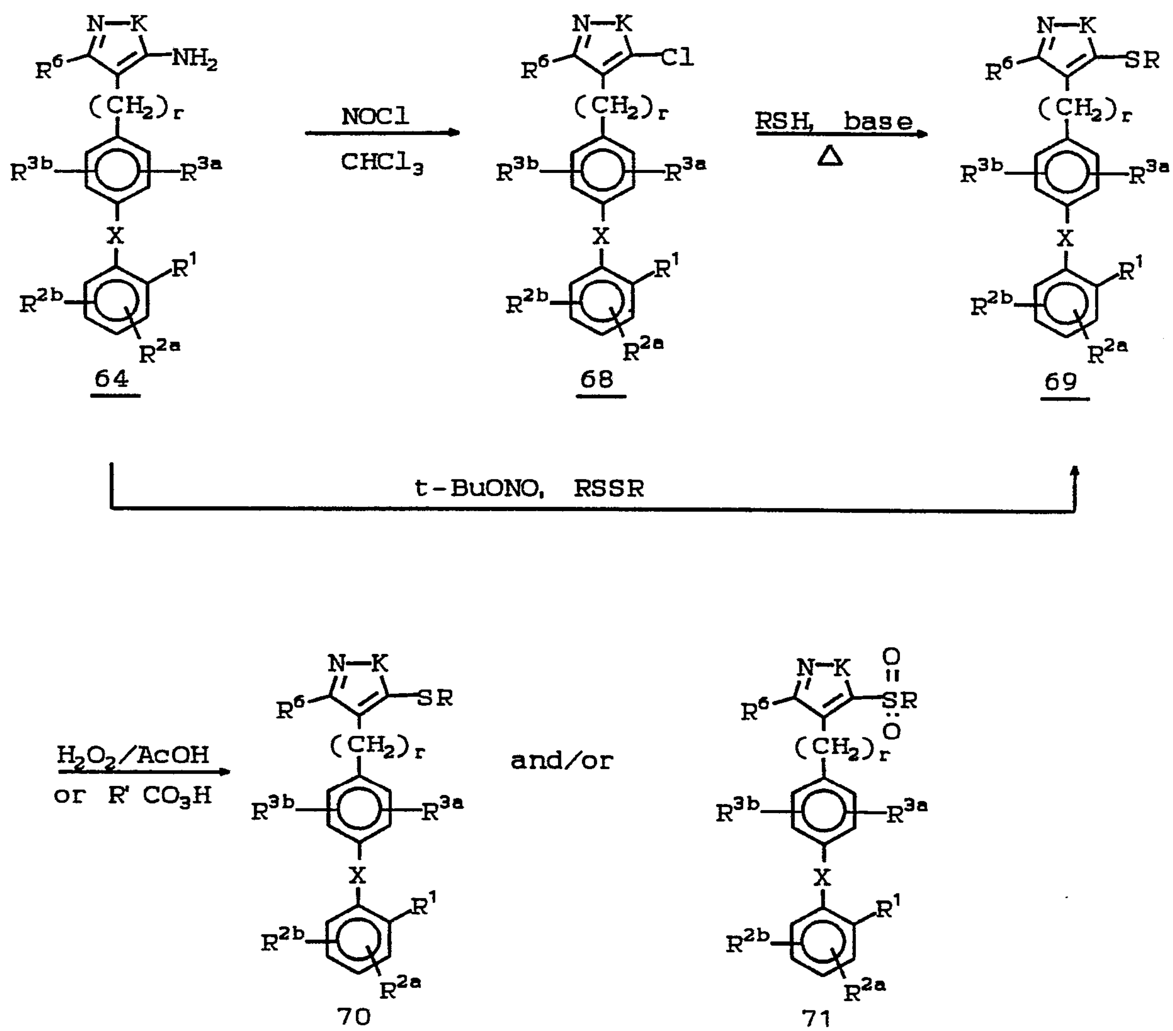
NOTE: R^1 may be protected prior to these reactions and deprotected subsequently

SCHEME 20



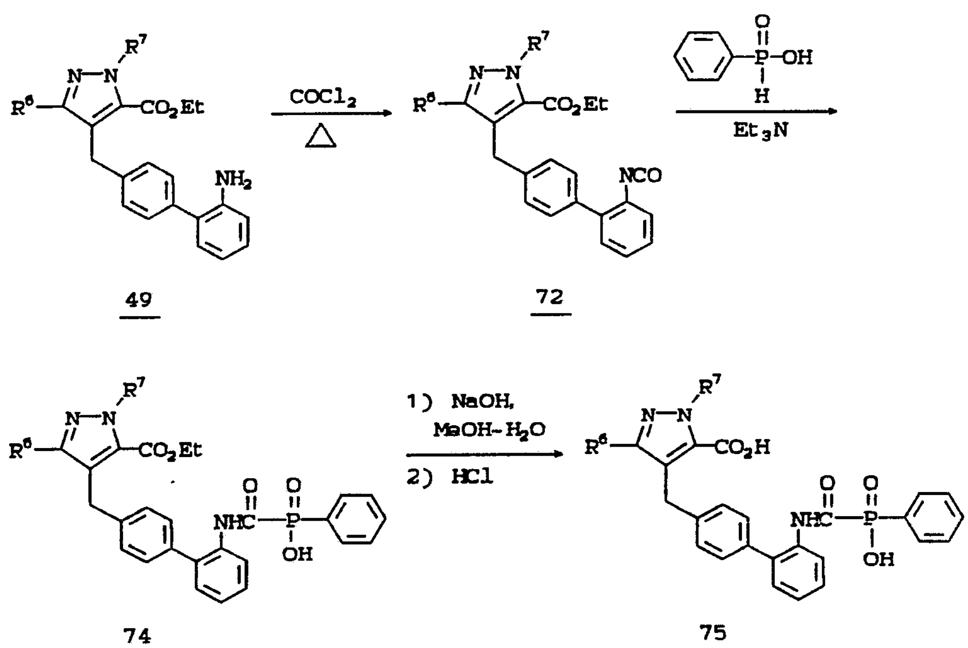
NOTE: R^1 may be protected prior to these reactions and deprotected subsequently

SCHEME 21

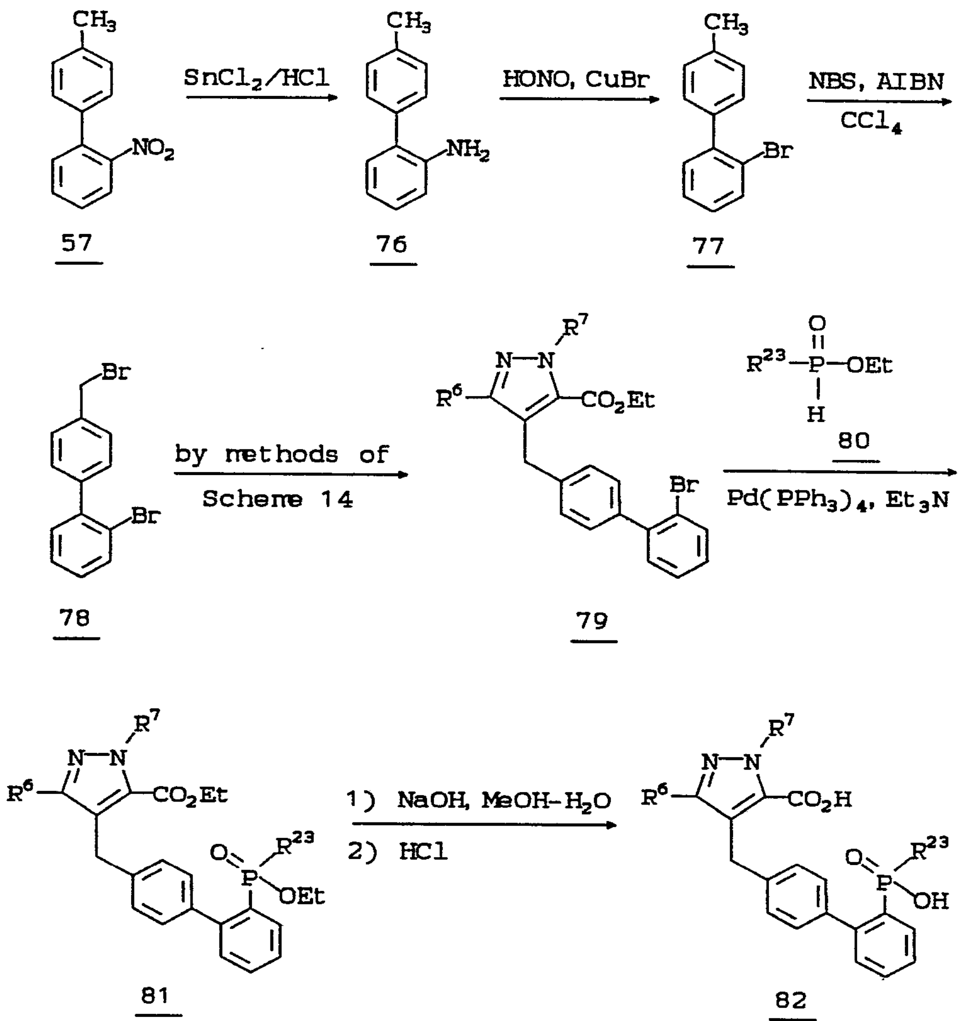


NOTE: R^1 may be protected prior to these reactions and deprotected subsequently

SCHEME 22


R7
N—N
R6
CO2Et
NH2
COCl2
NCO
P-OH
H
Et3N
49
72
1) NaOH,
MeOH-H2O
2) HCl
NHC
OH
CO2H
74
75

SCHEME 23


CH3
NO2
SnCl2/HCl
NH2
HONO, CuBr
Br
NBS, AIBN
CCl4
57
76
77
Br
by methods of
Scheme 14
R7
N—N
R6
CO2Et
Br
O
R23—P—OEt
H
80
Pd(PPh3)4, Et3N
78
79
CO2Et
O=P R23 OEt
1) NaOH, MeOH-H2O
2) HCl
CO2H
O=P R23 OH
81
82

The compounds of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkali metal salts like sodium and potassium salts, alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases; e.g., dicyclohexylamine salts, N-methyl-D-glucamine salts, salts with amino acids like arginine, lysine, and the like. Also, salts with organic and inorganic acids may be prepared; e.g., HCl, HBr, H_2SO_4, H_3PO_4, methanesulfonic, toluenesulfonic, maleic, fumaric, camphorsulfonic. The non-toxic, physiologically acceptable salts are preferred, although other salts are also useful, e.g., in isolating or purifying the product.

The salts can be formed by conventional means such as by reacting the free acid or free base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

Angiotensin II (AII) is a powerful arterial vasoconstrictor, and it exerts its action by interacting with specific receptors present on cell membranes. The compounds described in the present invention act as competitive antagonists of AII at the receptors. In order to identify AII antagonists and determine their efficacy in vitro, the following two ligand-receptor binding assays were established.

Receptor binding assay using rabbit aortae membrane preparation:

Three frozen rabbit aortae (obtained from Pel-Freeze Biologicals) were suspended in 5mM Tris-0.25M Sucrose, pH 7.4 buffer (50 ml), homogenized, and then centifuged. The mixture was filtered through a cheesecloth and the supernatant was centrifuged for 30 minutes at 20,000 rpm at 4°C. The pellet thus obtained was resuspended in 30 ml of 50mM Tris-5 mM $MgCl_2$ buffer containing 0.2% Bovine Serum Albumin and 0.2 mg/ml Bacitracin, and the suspension was used for 100 assay tubes. Samples tested for screening were done in duplicate. To the membrane preparation (0.25 ml) there was added ^{125}I-Sar^1Ile^8-angiotensin II [obtained from New England Nuclear] (10 µl; 20,000 cpm) with or without the test sample, and the mixture was incubated at 37°C for 90 minutes. The mixture was then diluted with ice-cold 50mM Tris-0.9% NaCl, pH 7.4 (4 ml) and filtered through a glass fiber filter (GF/B Whatman 2.4" diameter). The filter was soaked in scintillation cocktail (10 ml) and counted for radioactivity using Packard 2660 Tricarb liquid scintillation counter. The inhibitory concentration (IC_{50}) of potential AII antagonist, which gives 50% displacement of the total specifically bound ^{125}I-Sar^1Ile^8-angiotensin II, was presented as a measure of the efficacy of such compounds as AII antagonists.

Receptor assay using Bovine adrenal cortex preparation

Bovine adrenal cortex was selected as the source of AII receptor. Weighed tissue (0.1 g is needed for 100 assay tubes) was suspended in Tris.HCl (50mM), pH 7.7 buffer and homogenized. The homogenate was centrifuged at 20,000 rpm for 15 minutes. Supernatant was discarded and pellets resuspended in buffer [Na_2HPO_4 (10mM)-NaCl (120mM)-disodium EDTA (5mM) containing phenylmethane-sulfonyl fluoride (PMSF)(0.1mM)]. (For screening of compounds generally duplicates of tubes are used). To the membrane preparation (0.5 ml) there was added ^{3}H-angiotensin II (50 mM) (10 µl), with or without the test sample, and the mixture was incubated at 37°C for 1 hour. The mixture was then diluted with Tris buffer (4 ml) and filtered through a glass fiber filter (GF/B Whatman 2.4" diameter). The filter was soaked in scintillation cocktail (10 ml) and counted for radioactivity using Packard 2660 Tricarb liquid scintillation counter. The inhibitory concentration (IC_{50}) of potential AII antagonist, which gives 50% displacement of the total specifically bound ^{3}H-angiotensin II, was presented as a measure of the efficacy of such compounds as AII antagonists.

Using the methodology described above, representative compounds of the invention were evaluated and were found to exhibit an activity of at least $IC_{50} < 50 \mu M$, thereby demonstrating and confirming the utility of the compounds of the invention as effective AII antagonists.

The potential antihypertensive effects of the compounds described in the present invention may be evaluated using the methodology described below:

Male Charles River Sprague-Dawley rats (300-375 gm) were anesthetized with methohexital (Brevital; 50 mg/kg i.p.). The trachea was cannulated with PE 205 tubing. A stainless steel pithing rod (1.5 mm thick, 150 mm long) was inserted into the orbit of the right eye and down the spinal column. The rats were immediately placed on a Harvard Rodent Ventilator (rate - 60 strokes per minute, volume - 1.1 cc per 100 grams body weight). The right carotid artery was ligated, both left and right vagal nerves were cut, the left carotid artery was cannulated with PE 50 tubing for drug administration, and body temperature was maintained at 37°C by a thermostatically controlled heating pad which received input from a rectal temperature probe. Atropine (1 mg/kg i.v.) was then administered and 15 minutes later propranolol (1 mg/kg i.v.). Thirty minutes later antagonists of formula I were administered intravenously or orally. Angiotensin II was then typically given at 5, 10, 15, 30, 45 and 60 minute intervals and every half-hour thereafter for as long as the test compound showed activity. The change in the mean arterial blood pressure was recorded for each angiotensin II challenge and the percent inhibition of the angiotensin II response was calculated.

Thus, the compounds of the invention are useful in treating hypertension. They are also of value in the management of acute and chronic congestive heart failure, in the treatment of secondary hyperaldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and secondary pulmonary hypertension, renal failure such as diabetic nephropathy, glomerulonephritis, scleroderma, and the like, renal vascular hypertension, left ventricular dysfunction, diabetic retinopathy, and in the management of vascular disorders such as migraine, Raynaud's disease, luminal hyperplasia and to minimize the atherosclerotic process. The application of the compounds of this invention for these and similar disorders will be apparent to those skilled in the art.

The compounds of this invention are also useful to treat elevated intraocular pressure and can be administered to patients in need of such treatment with typical pharmaceutical formulations such as tablets, capsules, injectables and the like as well as topical ocular formulations in the form of solutions, ointments, inserts, gels, and the like. Pharmaceutical formulations prepared to treat intraocular pressure would typically contain about 0.1% to 15% by weight, preferably 0.5% to 2% by weight, of a compound of this invention.

In the management of hypertension and the clinical conditions noted above the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral adminis-

tration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. Although the dose will vary from patient to patient, depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication and other factors, which those skilled in the art will recognize, the dosage range will generally be about 1 to 1000 mg. per patient per day which can be administered in single or multiple doses. Perferably, the dosage range will be about 2.5 to 250 mg. per patient per day; more preferably about 2.5 to 75 mg. per patient per day.

The compounds of this invention can also be administered in combination with other antihypertensives such as diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers or ß-blockers. For example, the compounds of this invention can be given in combination with such compounds as amiloride, atenolol, bendroflumethiazide, chlorothalidone, chlorothiazide, clonidine, cryptenamine acetates and cryptenamine tannates, deserpidine, diazoxide, guanethidine sulfate, hydralazine hydrochloride, hydrochlorothiazide, metolazone, metoprolol tartate, methyclothiazide, methyldopa, methyldopate hydrochloride, minoxidil, pargyline hydrochloride, polythiazide, prazosin, propranolol, rauwolfia serpentina, rescinnamine,

reserpine, sodium nitroprusside, spironolactone, timolol maleate, trichlormethiazide, trimethophan camsylate, benzthiazide, quinethazone, ticrynafan, triamterene, acetazolamide, aminophylline, cyclothiazide, ethacrynic acid, furosemide, merethoxylline procaine, sodium ethacrynate, captopril, delapril hydrochloride, enalapril, enalaprilat, fosinopril sodium, lisinopril, pentopril, quinapril hydrochloride, ramapril, teprotide, zofenopril calcium, diflusinal, diltiazem, felodipine, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine, and the like, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly.

To illustrate these combinations, one of the angiotensin II antagonists of this invention effective clinically in the 2.5-250 milligrams per day range can be effectively combined at levels at the 0.5-250 milligrams per day range with the following compounds at the indicated per day dose range: hydrochlorothiazide (15-200 mg) chlorothiazide (125-2000 mg), ethacrynic acid (15-200 mg),amiloride (5-20 mg), furosemide (5-80 mg), propranolol (20-480 mg), timolol maleate (5-60 mg.), methyldopa (65-2000 mg), felodipine (5-60 mg), nifedipine (5-60 mg), and nitrendipine (5-60 mg). In addition, triple drug combinations of hydrochlorothiazide (15-200 mg) plus amiloride (5-20 mg) plus

angiotensin II antagonist of this invention (3-200 mg) or hydrochlorothiazide (15-200 mg) plus timolol maleate (5-60) plus an angiotensin II antagonist of this invention (0.5-250 mg) or hydrochlorothiazide (15-200 mg) and nifedipine (5-60 mg) plus an angiotensin II antagonist of this invention (0.5-250 mg) are effective combinations to control blood pressure in hypertensive patients. Naturally, these dose ranges can be adjusted on a unit basis as necessary to permit divided daily dosage and, as noted above, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors.

Typically, these combinations can be formulated into pharmaceutical compositions as discussed below.

About 1 to 100 mg. of compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which can be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium

stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unitform is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The useful central nervous system (CNS) activities of the compounds of this invention are demonstrated and exemplified by the ensuing assays.

COGNITIVE FUNCTION ASSAY

The efficacy of these compounds to enhance cognitive function can be demonstrated in a rat passive avoidance assay in which cholinomimetics such as physostigmine and nootropic agents are known to be active. In this assay, rats are trained to inhibit

their natural tendency to enter dark areas. The test apparatus used consists of two chambers, one of which is brightly illuminated and the other is dark. Rats are placed in the illuminated chamber and the elapsed time it takes for them to enter the darkened chamber is recorded. On entering the dark chamber, they receive a brief electric shock to the feet. The test animals are pretreated with 0.2 mg/kg of the muscarinic antagonist scopolamine which disrupts learning or are treated with scopolamine and the compound which is to be tested for possible reversal of the scopolamine effect. Twenty-four hours later, the rats are returned to the illuminated chamber. Upon return to the illuminated chamber, normal young rats who have been subjected to this training and who have been treated only with control vehicle take longer to re-enter the dark chamber than test animals who have been exposed to the apparatus but who have not received a shock. Rats treated with scopolamine before training do not show this hesitation when tested 24 hours later. Efficacious test compounds can overcome the disruptive effect on learning which scopolamine produces. Typically, compounds of this invention should be efficacious in this passive avoidance assay in the dose range of from about 0.1 mg/kg to about 100 mg/kg.

ANXIOLYTIC ASSAY

The anxiolytic activity of the invention compounds can be demonstrated in a conditioned emotional response (CER) assay. Diazepam is a

clinically useful anxiolytic which is active in this assay. In the CER protocol, male Sprague-Dawley rats (250-350 g) are trained to press a lever on a variable interval (VI) 60 second schedule for food reinforcement in a standard operant chamber over weekly (five days per week) training sessions. All animals then receive daily 20 minute conditioning sessions, each session partitioned into alternating 5 minute light (L) and 2 minute dark (D) periods in a fixed L1D1L2D2L3 sequence. During both periods (L or D), pressing a lever delivers food pellets on a VI 60 second schedule: in the dark (D), lever presses also elicit mild footshock (0.8 mA, 0.5 sec) on an independent shock presentation schedule of VI 20 seconds. Lever pressing is suppressed during the dark periods reflecting the formation of a conditioned emotional response (CER).

Drug testing in this paradigm is carried out under extinction conditions. During extinction, animals learn that responding for food in the dark is no longer punished by shock. Therefore, response rates gradually increase in the dark periods and animals treated with an anxiolytic drug show a more rapid increase in response rate than vehicle treated animals. Compounds of this invention should be efficacious in this test procedure in the range of from about 0.1 mg/kg to about 100 mg/kg.

DEPRESSION ASSAY

The antidepressant activity of the compounds of this invention can be demonstrated in a tail suspension test using mice. A clinically useful antidepressant which serves as a positive control in this assay is desipramine. The method is based on the observations that a mouse suspended by the tail shows alternate periods of agitation and immobility and that antidepressants modify the balance between these two forms of behavior in favor of agitation. Periods of immobility in a 5 minute test period are recorded using a keypad linked to a microcomputer which allows the experimenter to assign to each animal an identity code and to measure latency, duration and frequency of immobile periods. Compounds of this invention should be efficacious in this test procedure in the range of from about 0.1 mg/kg to about 100 mg/kg.

SCHIZOPHRENIA ASSAY

The antidopaminergic activity of the compounds of this invention can be demonstrated in an apomorphine-induced stereotypy model. A clinically useful antipsychotic drug that is used as a positive control in this assay is haloperidol. The assay method is based upon the observation that stimulation of the dopaminergic system in rats produces stereotyped motor behavior. There is a strong correlation between the effectiveness of classical neuroleptic drugs to block apomorphine-induced stereotypy and to prevent schizophrenic symptoms. Stereotyped behavior

induced by apomorphine, with and without pretreatment with test compounds, is recorded using a keypad linked to a microcomputer. Compounds of the invention should be efficacious in this assay in the range of from about 0.1 mg/kg to about 100 mg/kg.

In the treatment of the clinical conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. Although the dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize, the dosage range will generally be about 5 to 6000 mg. per patient per day which can be administered in single or multiple doses. Preferably, the dosage range will be about 10 to 4000 mg. per patient per day; more preferably about 20 to 2000 mg. per patient per day.

In order to obtain maximal enhancement of cognitive function, the compounds of this invention may be combined with other cognition-enhancing agents. These include acetylcholinesterase inhibitors such as heptylphysostigmine and tetrahydroacridine (THA; tacrine), muscarinic agonists such as

oxotremorine, inhibitors of angiotensin-converting enzyme such as octylramipril, captopril, ceranapril, enalapril, lisinopril, fosinopril and zofenopril, centrally-acting calcium channel blockers and as nimodipine, and nootropic agents such as piracetam.

In order to achieve optimal anxiolytic activity, the compounds of this invention may be combined with other anxiolytic agents such as alprazolam, lorazepam, diazepam, and buspirone.

In order to achieve optimal antidepressant activity, combinations of the compounds of this invention with other antidepressants are of use. These include tricyclic antidepressants such as nortriptyline, amitryptyline and trazodone, and monoamine oxidase inhibitors such as tranylcypromine.

In order to obtain maximal antipsychotic activity, the compounds of this invention may be combined with other antipsychotic agents such as promethazine, fluphenazine and haloperidol.

The following examples illustrate the preparation of the compounds of formula (I) and their incorporation into pharmaceutical compositions and as such are not to be considered as limiting the invention set forth in the claims appended hereto. All reactions as appropriate were carried out under an atmosphere of dry nitrogen under standard conditions for those skilled in the art.

EXAMPLE 1

5-AMINO-3-BUTYL-4-[(2'-(TETRAZOL-5-YL)BIPHEN-4-YL)-METHYL]ISOXAZOLE

A: 2-Cyano-4'-methylbiphenyl

To a solution of p-bromotoluene (30 g) in dry ether (150 ml) at -78°C, a solution of t-BuLi in pentane (1.7M) (210 ml) was added slowly over a period of 1.5 hr, using a dropping funnel. The bath was then removed and the mixture was stirred at room temperature for an additional 2 hr. The contents of the flask was then added slowly (using a cannula) at room temperature to a premixed solution of $ZnCl_2$ in ether (1M) (180 ml) and dry THF (360 ml). The mixture was stirred for 2h at that temperature and then the slurry was added (using a cannula) to a solution of 2-bromobenzonitrile (21.3 g) and $NiCl_2(Ph_3P)_2$ (2.1 g) in dry THF (300 ml). The mixture, after stirring at room temperature overnight (18 h), was poured slowly under stirring into ice-cold 1N HCl (1500 ml). The organic layer was separated, and the aqueous phase was extracted with ether (3 X 300 ml). The combined organic layer was washed with water, brine and then dried over $MgSO_4$. Removal of the solvent gave the crude product as a semisolid mass (34 g). The material was purified on a silica-gel flash column using ethyl acetate-hexane (1:12) to give the desired nitrile as a low-melting solid (28 g, 88%). ^1H NMR ($CDCl_3$): 2.42 (s, 3H), 7.2-7.8 (m, 8H); FAB-MS: m/e 194 (M^++1).

B: Trimethylstannyl azide

To a concentrated solution of NaN_3 (1.2 kg, 18.5 moles) in water (3 L), a solution of trimethyltin chloride (600 g, 3 moles) in dioxane (400 ml) was added in three portions under vigorous stirring. A precipitate formed instantaneously. The mixture, after stirring overnight at room temperature, was filtered. The residue was washed with water and dried under suction and then in vacuo over P_2O_5. Yield 541 g (88%), mp 120-122°C.

C: 5-[2-(4'-Methylbiphenyl)]tetrazole

To a solution of 2-cyano-4'-methylbiphenyl (Step A) (390 g, 2.02 moles) in toluene (2.3 L) was added trimethyltin azide (Step B) (525 g, 2.55 moles) at r.t. The mixture was refluxed for 24 h, cooled to r.t., filtered, washed with toluene and sucked dry in a funnel. The precipitate was resuspended in toluene (3.5 L) and THF (250 mL) was added. Anhydrous HCl was bubbled in at a moderate rate at r.t. to give a clear solution (45 min). Addition of HCl gas was continued for another 20 min. with stirring whereupon a white precipitate formed. The reaction mixture was stirred over night. The solid product was filtered, washed with toluene followed with ether and then dried under vacuum. This produced 250 g (53% yield of the tetrazole. m.p. 152-154°C; ^{1}H-NMR ($CDCl_3$):2.40 (s, 3H), 7.19 (dd, 1H), 7.55 (m, 2H), 8.25 (dd, 1H).

D: N-Triphenylmethyl-5-[2-(4'-methylbiphenyl)]-tetrazole

To a cloudy solution of 5-[2-(4'-methylbiphenyl)]tetrazole (Step C) (250 g, 1.06 mole) in CH_2Cl_2 (4 L) was added triphenylmethylchloride (310 g 1.11 mole) at r.t. The reaction mixture was stirred and triethylamine (190 mL, 138 g, 1.36 mole) was added portionwise. After addition, the mixture was stirred at reflux for 90 min. The solution was cooled to r.t., washed with water (2x1L)and dried over $MgSO_4$, filtered through a silica gel plug and concentrated on the rotovap to a solid. This was crystallized from toluene to give the product as an off-white solid (425 g, 84%); m.p. 166-168 ^oC; ^1H-NMR ($CDCl_3$): 2.28 (s, 3H), 6.9-7.05 (m, 10H), 7.2-7.5 (m, 12H), 7.9 (dd, 1H).

E: N-Triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)] tetrazole

To a solution of N-triphenylmethyl-5-[2-(4'-methylbiphenyl)] tetrazole (Step D) (425 g, 0.89 moles) in CCl_4 (4.0 L) were added N-bromsuccinimide (159 g, 0.89 mole) and dibenzoyl peroxide (22 g, 0.089 moles). The mixture was refluxed for 2 hours, cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* to give a thick oil. The addition of ether (2.0 L) to this oil resulted in a clear solution. Crystallization, followed by filtration, gave a white solid (367 g, 74%). m.p. 137-139.5^oC; ^1H-NMR ($CDCl_3$): 4.38 (s, 2H), 6.9-8.0 (m, 23H).

F: 3-Oxoheptanenitrile

To a mechanically stirred solution of 14.3 g $MgSO_4$-dried cyanoacetic acid and ~100 mg 1,10-phenanthroline in 500 mL THF at -78°C was added 60 mL 2.5 M n-butyllithium in hexanes (~one half of the total). The indicator color persisted at this point. The solution was warmed to -5° to +5°C after which the indicator color disappeared. Another 55 mL 2.5 M n-butyllithium in hexanes was added until the indicator color again persisted. The mixture was cooled to -78°C then 10.0 mL valeryl chloride was added over 3 minutes. After 10 minutes the now yellow solution was allowed to warm to room temperature and stir for 1 hour. The mixture was poured into a solution of 50 mL concentrated HCl in 300 mL water. The mixture was extracted 3 times with ether. The combined organic material was washed twice with saturated $NaHCO_3$ solution then once with brine. The washes were back extracted with ether and the back extracts were washed with brine. The back extracts were combined with the other organic material and then were dried over $MgSO_4$. The organic material was stripped of solvent in vacuo and was then distilled at ~1 Torr with the title compound distilling at 87-91°C. The title compound was isolated as a clear oil, 6.32 g, 60% yield. To this material there was added 1% by weight BHT to prevent polymerization. The material was also refrigerated to prevent polymerization. R_f 0.18 in 20% EtOAc/hexane, visualized by ninhydrin stain;

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.46 (s, 2H), 2.62 (3 line m, 2H), 1.61 (m, 2H), 1.35 (m, 2H), 0.92 (t, J=7.3Hz, 3H); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 197.6, 113.8, 41.9, 31.9, 25.3, 22.0, 13.7.

G: <u>2-[(2'-(N-Triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]-3-oxoheptanenitrile</u>

To a solution of 225 mg of ethyl 3-oxoheptanenitrile (Step F) in 10 mL of DMSO was added 144 mg of 60% NaH in oil. After two minutes, 500 mg of N-triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)]-tetrazole (Step E) was added all at once to the solution. After 20 minutes the solution was poured into brine and extracted 3 times with ether. The organic material was dried over $MgSO_4$, stripped of solvent <u>in vacuo</u>, and MPLC'd in 15% EtOAc/hexane. The title compound was isolated as a white foam, 125 mg, 23% yield. R_f 0.23 in 20% EtOAc/hexane, visualized by UV and ammonium molybdate/ceric sulfate stain; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.93 (m, 1H), 7.47 (10 line m, 2H), 7.40-7.20 (m, 10H), 7.04 (m, 4H), 6.90 (m, 6H), 3.44 (X of ABX, 1H), 3.03 (AB of ABX, J_{AB}=13.8 Hz, J_{AX}=8.6 Hz, J_{BX}=5.3 Hz, Δν=43.5 Hz, 2H), 2.59 (sym. 12 line m, 2H), 1.55 (m, 2H), 1.28 (m, 2H), 0.88 (t, J=7.3 Hz, 3H).

H: <u>5-Amino-3-butyl-4-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]isoxazole</u>

A solution of 60 mg of 2-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]-3-oxoheptanenitrile (Step G), 17 mg of hydroxylamine hydrochloride, and 100 μL of pyridine in 3 mL of

ethanol was heated to reflux for two hours. The mixture was cooled to room temperature and was stripped of solvent in vacuo. The crude material was MPLC'd in concentrated NH_4OH/EtOAc/hexane to give the title compound.

I: 5-Amino-3-butyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]isoxazole

The title compound may be obtained by stirring 5-amino-3-butyl-4-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]isoxazole (Step H) in methanol with excess concentrated HCl at room temperature. After 15 minutes, an indicator quantity of phenolphthalein is added followed by 10% NaOH until pink. Acetic acid is added to pH 5 and the mixture is stripped of most of its solvent in vacuo. The remainder is partitioned between brine and ether or methylene chloride. The aqueous layer is extracted twice more. The combined organic material is dried over $MgSO_4$ or Na_2SO_4, stripped of solvent in vacuo, then column chromatographed to give the title compound.

EXAMPLE 2

5-AMINO-3-BUTYL-1-(2'-CHLOROPHENYL)-4-[(2'-TETRAZOL-5-YL)BIPHEN-4-YL)METHYL]PYRAZOLE

A mixture of 61 mg 2-[(2'-(N-triphenyl-methyltetrazol-5-yl)biphen-4-yl)methyl]-3-oxoheptane-nitrile, (Example 1, Step G) 20 mg o-chlorophenyl-hydrazine, and 10 mg NaOAc in 5 mL xylenes was heated to reflux for one hour. The volatile materials were

removed in vacuo. The crude material was redissolved in methanol and 20 drops concentrated HCl was added. After 30 minutes phenolphthalein was added and 10% NaOH was added until pink. The mixture was reacidified with about 500 µL acetic acid. Most of the volatiles were removed in vacuo. Brine was added and the mixture was extracted three times with ether. The combined organic material was dried over $MgSO_4$, stripped of solvent in vacuo, and MPLC'd in 1/55/44 acetic acid/ethyl acetate/hexane to give 11 mg of the title compound. R_f 0.17 in 1/60/39 acetic acid/ethyl acetate/hexane; ^1H-NMR (300 MHz, $CDCl_3$): δ 7.87 (d, 1H), 7.70-6.98 (m, 11H), 3.74 (s, 2H), 2.18 (3 line m, 2H), 1.53 (m, 2H), 1.31 (m, 2H), 0.88 (t, 3H).

EXAMPLE 3

3-BUTYL-1-(2-CHLOROPHENYL)-4-[[2'-(5-TETRAZOLYL]-BIPHENYL-4-YL]METHYL]-1H-PYRAZOLE-5-CARBOXYLIC ACID

A: 3-Butyl-5-chloro-1-(2'chlorophenyl)-4-[(2'(n-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]-pyrazole

A solution of 5-amino-3-butyl-1-(2'-chlorophenyl)-4-[(2'-(N-triphenylmethyl-tetrazol-5-yl)-biphen-4-yl)methyl]pyrazole (Example 2) in CCl_4 is diazotized according to the procedure in Japanese Patent 1,100,570 to give the title compound.

B: 3-Butyl-1-(2-chlorophenyl)-4-[[2'-(5-tetrazolyl]-biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

A solution of 5-chloro-3-butyl-1-(2'-chlorophenyl)-4-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methylpyrazole (Step A) and sodium cyanide in DMSO is heated. The resulting solution nitrile pyrazole diluted with brine and extracted with ether. The crude product may be hydrolyzed with 50% H_2SO_4 with warming to give the title compound.

EXAMPLE 4

ETHYL 3-BUTYL-1-PHENYL-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]METHYL]-1H-PYRAZOLE-5-CARBOXYLATE

A: Ethyl 2-methoxyimino-4-oxooctanoate

A mixture of 7.00 g (35 mmole) of ethyl 2,4-dioxooctanoate [K. Seki, J. Isegawa, M. Fukuda, and M. Ohki, *Chem. Pharm. Bull.*, 32 1568 (1984)], 3.07 g (36.75 mmole) of methoxyamine hydrochloride, 35 g of 3Å molecular sieves, and 35 ml of dry EtOH was stirred vigorously at room temperature in a stoppered flask. After 21.5 hours, the mixture was filtered, and the filter cake was washed with EtOH. The combined filtrate and washings were concentrated *in vacuo* at ≤ 35°C. The residue was partitioned between 100 ml of Et_2O and 100 ml of saturated aqueous $NaHCO_3$ solution. The Et_2O layer was washed with 2 x 100 ml of H_2O, then filtered to remove some insoluble solid, and re-separated. The Et_2O phase was dried over $MgSO_4$, filtered, and concentrated in vacuo at < 30°C to give a reddish-orange residual oil. This material was chromatographed twice on silica gel (gradient elution, first with 3-7.5% and then 3-10% EtOAc in hexane) to yield, after vacuum-drying at room temperature, 4.14 g (52%) of very pale yellow residual oil, homogeneous by TLC in 4:1 hexane-EtOAc. 400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.88 (t, 3H), 1.2-1.35 (m, 5H), 1.54 (m, 2H), 2.45 (t, 2H), 3.68 (s, 2H), 4.03 (s, 3H), 4.31 (q, 2H). FAB-MS: m/e 230 $(M+H)^+$.

Analysis ($C_{11}H_{19}NO_4$)
Calcd: C, 57.62; H, 8.35; N, 6.11
Found: C, 57.65; H, 8.05; N, 6.05

Note: In a similar preparation, the higher R_f contaminant (removed by column chromatography) was isolated in 8% yield and identified as ethyl 2,4-bis(methoxyimino)octanoate, which by NMR appeared to exist as a pair of syn- and anti-isomers.
300 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.89 (apparent dt, 3H), 1.2-1.35 (m, 5H), 1.45 (m, 2H), 2.18,2.26 (t, total 2H), 3.34 (apparent d, 2H), 3.74 (apparent d, 3H), 4.04 (apparent d, 3H). 4.32 (apparent dq, 2H). FAB-MS: 259 $(M+H)^+$.

B: Ethyl 3-[(2'-cyanobiphenyl-4-yl)methyl]-2-methoxyimino-4-oxooctanoate

A mixture of 4.08 g (17.8 mmole) of ethyl 2-methoxyimino-4-oxooctanoate (from Step A), 5.70 g (17.8 mmole, based on 85% purity) of 4-bromomethyl-2'-cyanobiphenyl (EP 253,310), 2.95 g (21.4 mmole) of freshly pulverized anhydrous K_2CO_3, and 50 ml of dry DMF was stirred vigorously at room temperature under N_2. After 24 hours, the mixture was partititoned between 1 L. of EtOAc and 1 L. of 0.2 N HCl. The EtOAc phase was washed with 3 x 1 L of H_2O, then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The viscous residual oil was dissolved in CH_2Cl_2 and evaporated onto silica gel (just enough to give a free-flowing powder). This was added as a slurry in hexane to the top of a column of silica gel (74 x 6 cm) packed in hexane. Gradient elution with

5-10% EtOAc in hexane yielded 4.56 g (61%) of colorless residual gum, suitable for use but containing a trace of higher R_f impurity by TLC in 4:1 hexane-EtOAc.
400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.86 (t, 3H), 1.5-1.3 (m, 5H, including t at 1.23), 1.53 (m, 2H), 2.31 (t, 2H), 2.98 (dd, 1H), 3.42 (dd, 1H), 3.98 (s, 3H). 4.15-4.3 (m, 3H), 7.23 (d, 2H), 7.35-7.5 (m, 4H), 7.60 (m, 1H), 7.72 (d, 1H). FAB-MS: m/e 421 $(M+H)^+$.

After prolonged standing at room temperature, the remaining material had partially crystallized and was induced to crystallize fully upon trituration with petroleum ether. The material was collected on a filter and washed with some additional petroleum ether. After vacuum drying at room temperature, there was obtained 3.76 g (projected yield 56%) of white crystals, mp 62-63°C., homogeneous by TLC in 4:1 hexane-EtOAc.
Analysis ($C_{25}H_{28}N_2O_4$)
Calcd: C, 71.40; H, 6.71; N, 6.66
Found: C, 71.38; H, 6.64; N, 6.60

C: Ethyl 3-Butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-1-phenyl-1H-pyrazole-5-carboxylate

A mixture of 210 mg (0.5 mmole) of ethyl 3-[(2'-cyanobiphenyl-4-yl)methyl]-2-methoxyimino-4-oxooctanoate (from Step B), 219 mg (1.5 mmole) of phenylhydrazine hydrochloride, 4 ml of glacial acetic acid, and 2 ml of 2-methoxyethanol was stirred under N_2 at 105°C for 40 hours. After combination with two similar 0.025 mmole-scale reactions, the mixture was

concentrated *in vacuo* at ≤ 50°C. The residue was partitioned between 20 ml of EtOAc and 20 ml of 0.2 N HCl. The EtOAc phase was washed with 20 ml of H_2O, then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residual oil was dissolved in CH_2Cl_2 and evaporated onto silica gel (just enough to give a free flowing powder). This was added as a slurry in hexane to a column of silica gel (40 x 2.4 cm) packed in hexane. Elution with 95:5 hexane-EtOAc followed by 90:10 hexane-EtOAc yielded (after vacuum-drying) 169 mg (66%) of golden-yellow residual gum, homogeneous by TLC in 4:1 hexane-EtOAc. 400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.86 (t, 3H), 1.03 (t, 3H, 1.33 (m, 2H), 1.57 (m, 2H), 2.61 (t, 2H), 4.12 (q, 2H), 4.17 (s, 2H). 7.29 (d, 2H), 7.35-7.5 (m, 9H), 7.60 (dd, 1H), 7.73 (d, 1H). FAB-MS: m/e 464 $(M+H)^+$.

Analysis ($C_{30}H_{29}N_3O_2$)

Calcd: C, 77.73; H, 6.31; N, 9.06

Found: C, 77.49; H, 6.09; N, 8.81

D: Ethyl 3-Butyl-1-phenyl-4-[(2'-(5-tetrazolyl)-biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

To 116 mg (0.25 mmole) of ethyl 3-butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-1-phenyl-1H pyrazole-5-carboxylate (from Step C) were added 180 mg (0.875 mmole) of trimethyltin azide (Example 1, Step B) and 1.2 ml of dry toluene. The mixture was stirred at reflux under N_2 for 39 hours, then cooled, and concentrated *in vacuo*. The residual gum was treated with 1.2 g of silica gel and 3.6 ml of dry MeOH. The mixture was stirred overnight in a

stoppered flask and then concentrated _in vacuo_ at < 30°C. The residual powder was added as a slurry in CH_2Cl_2 to the top of a column of silica gel (24 x 2.3 cm) packed in CH_2Cl_2. Gradient elution with 1-4% MeOH in CH_2Cl_2 afforded (after vacuum-drying at 50°C.) 95.9 mg (76%) of pale yellow, stiff foam, mp >60°C. (gradual); homogeneous by TLC in 19:1 CH_2Cl_2-MeOH.

400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.88 (t, 3H), 0.99 (t, 3H, 1.35 (m, 2H), 1.59 (m, 2H), 2.58 (t, 2H), 4.09 (q, 2H), 4.15 (s, 2H). 7.14 (d, 2H), 7.24 (d, 2H), 7.3-7.6 (m, 8H), 8.17 (d, 1H) FAB-MS: m/e 507 $(M+H)^+$.

Analysis ($C_{30}H_{30}N_6O_2$)

Calcd: C, 71.12; H, 5.97; N, 16.59

Found: C, 70.96; H, 5.99; N, 16.50

EXAMPLE 5

3-BUTYL-1-PHENYL-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]-METHYL]-1H-PYRAZOLE-5-CARBOXYLIC ACID

A solution of 70.6 mg (0.139 mmole) of ethyl 3-butyl-1-phenyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1_H_-pyrazole-5-carboxylate (from Example 4) in 1.1 ml of MeOH was treated with 0.55 ml (1.4 mmole) of 2.5 _N_ NaOH. The resulting solution was stirred under N_2 in an oil bath at 60°C for 21 hours. The cooled solution was filtered, diluted with 10 ml of H_2O, and acidified to pH < 2 by gradual addition of 2 _N_ HCl, resulting in precipitation. After a few minutes, the precipitate was collected on a filter and washed thoroughly with dilute HCl (pH

2). The solid was sucked dry overnight on the filter and then dried in vacuo ($\leq$ 1 mm) at 75°C for several hours to yield 62.3 mg (92%) of white powder, mp > 115°C (gradual; preliminary softening); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^1H NMR (DMSO-d_6): δ (ppm) 0.79 (t, 3H), 1.24 (m, 2H), 1.41 (m, 2H), 2.45 (t, 2H), 4.05 (s, 2H), 6.99 (d, 2H), 7.12 (d, 2H), 7.35-7.7 (m, 9H), FAB-MS: m/e 479 $(M+H)^+$.
Analysis ($C_{28}H_{26}N_6O_2 \bullet 0.6H_2O$)
Calcd: C, 68.72; H, 5.60; N, 17.18
Found: C, 68.67; H, 5.64; N, 17.17

EXAMPLE 6

ETHYL 3-BUTYL-1-(2-CHLOROPHENYL)-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]METHYL]-1H-PYRAZOLE-5-CARBOXYLATE

A: Ethyl 3-butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-1-(2-chlorophenyl)-1H-pyrazole-5-carboxylate

Reaction of ethyl 3-[(2'-cyanobiphenyl-4-yl)methyl]-2-methoxyimino-4-oxooctanoate (Example 4, Step B) with 2-chlorophenylhydrazine hydrochloride according to the procedure of Example 4, Step C, gave a 73% yield of the title compound as a yellow-orange gum; nearly homogeneous by TLC in 4:1 hexane-EtOAc. 400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.85 (t, 3H), 1.32 (m, 2H), 1.58 (m, 2H), 2.61 (t, 2H), 4.11 (br q, 2H), 4.23 (s, 2H), 7.28 (d, 2H), 7.35-7.5 (m, 8H), 7.61 (dd, 1H), 7.73 (d, 1H). FAB-MS: m/e 498 $(M+H)^+$.

Analysis ($C_{30}H_{28}ClN_3O_2 \bullet 0.1CH_2Cl_2$)
Calcd: C, 71.37; H, 5.61; N, 8.30
Found: C, 71.31; H, 5.45; N, 8.10

B: Ethyl 3-butyl-1-(2-chlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1*H*-pyrazole-5-carboxylate

The product from Step A was converted to the title compound by the procedure of Example 4, Step D, in 65% yield as a pale yellow, stiff foam, mp >70°C. (gradual); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.87 (t, 3H), 0.96 (t, 3H), 1.34 (m, 2H), 1.60 (m, 2H), 2.61 (t, 2H), 4.08 (br q, 3H), 4.22 (s, 2H), 7.16 (d, 2H), 7.25 (d, 2H), 7.3-7.6 (m, 7H), 8.21 (d, 1H). FAB-MS: m/e 498 $(M+H)^+$.
Analysis ($C_{30}H_{29}ClN_6O_2$)
Calcd: C, 66.59; H, 5.40; N, 15.53
Found: C, 66.38; H, 5.56; N, 15.31

EXAMPLE 7

3-BUTYL-1-(2-CHLOROPHENYL)-4-[[2'-(5-TETRAZOLYL)-BIPHENYL-4-YL]METHYL]-1H-PYRAZOLE-5-CARBOXYLIC ACID

By the method of Example 5, ethyl 3-butyl-1-(2-chlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1*H*-pyrazole-5-carboxylate (Example 6) was converted in 96% yield to the title compound as a nearly white solid, mp > 125°C (gradual; preliminary softening); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^1H NMR (DMSO-d_6): δ (ppm) 0.78 (t, 3H), 1.22

(m, 2H), 1.42 (m, 2H), 2.45 (t, 2H), 4.11 (s, 2H), 7.01 (d, 2H), 7.10 (d, 2H), 7.4-7.7 (m, 8H). FAB-MS: m/e 513 $(M+H)^+$.

Analysis ($C_{28}H_{25}ClN_6O_2 \bullet 0.5H_2O$)

Calcd: C, 64.42; H, 5.02; N, 16.10

Found: C, 64.50; H, 5.19; N, 15.91

EXAMPLE 8

ETHYL 3-BUTYL-1-(2-METHYLPHENYL)-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]METHYL]-1*H*-PYRAZOLE-5-CARBOXYLATE

A: Ethyl 3-butyl-4-[(2'-cyanobiphenyl-4-yl]methyl]-1-(2-methylphenyl)-1H-pyrazole-5-carboxylate

Reaction of ethyl 3-[(2'-cyanobiphenyl-4-yl)-methyl]-2-methoxyimino-4-oxooctanoate (Example 4, Step B) with *o*-methylphenylhydrazine hydrochloride according to the procedure of Example 4, Step C, yielded 70% of the title compound as a light orange gum; homogeneous by TLC in 4:1 hexane-EtOAc. 400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.85 (t, 3H), 0.96 (t, 3H), 1.32 (m, 2H), 1.58 (m, 2H), 2.03 (s, 3H), 2.62 (t, 2H), 4.05 (q, 2H), 4.21 (s, 2H), 7.2-7.5 (m, 10H), 7.61 (dd, 1H), 7.73 (d, 1H) FAB-MS: m/e 478 $(M+H)^+$.

Analysis ($C_{31}H_{31}N_3O_2$)

Calcd: C, 77.96; H, 6.54; N, 8.80

Found: C, 77.67; H, 6.55; N, 8.57

B: Ethyl 3-butyl-1-(2-methylphenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

By the procedure of Example 5, Step D, the product from Step A (above) was converted in 69% yield to the title compound as a nearly colorless glass, mp >60°C (gradual); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.88, 0.91 (overlapping t, each 3H), 1.34 (m, 2H), 1.60 (m, 2H), 2.00 (s, 3H), 2.60 (t, 2H), 4.03 (q, 2H), 4.20 (s, 2H), 7.1-7.6 (m, 11H), 8.17 (d, 1H) FAB-MS: m/e 521 $(M+H)^+$.

Analysis ($C_{31}H_{32}N_6O_2 \bullet 0.1\ CH_2Cl_2$)
Calcd: C, 70.59; H, 6.13; N, 15.89
Found: C, 70.27; H, 6.16; N, 15.86

EXAMPLE 9

3-BUTYL-1-(2-METHYLPHENYL)-4-[[2'-(5-TETRAZOLYL)-BIPHENYL-4-YL]METHYL-1H-PYRAZOLE-5-CARBOXYLIC ACID

Ethyl 3-butyl-1-(2-chlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate (Example 8) was saponified according to the procedure of Example 5 to give a 91% yield of the title compound as a white powder, mp >125°C. (gradual; preliminary softening); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^1H NMR (DMSO-d_6): δ (ppm) 0.78, (t, 3H), 1.22 (m, 2H), 1.42 (m, 2H), 1.94 (s, 3H), 2.45 (t, 2H), 4.10 (s, 2H), 7.00 (d, 2H), 7.10 (d, 2H), 7.2-7.4 (m, 4H), 7.5-7.7 (m, 4H). FAB-MS: m/e 493 $(M+H)^+$.

Analysis ($C_{29}H_{28}N_6O_2 \bullet 0.6\ H_2O$)
Calcd: C, 69.19; H, 5.85; N, 16.70
Found: C, 69.35; H, 5.62; N, 16.37

EXAMPLE 10

ETHYL 3-BUTYL-1-(2,6-DICHLOROPHENYL)-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]METHYL]-1*H*-PYRAZOLE-5-CARBOXYLATE

A: Ethyl 3-butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-1-(2,6-dichlorophenyl)-1H-pyrazole-5-carboxylate

Ethyl 3-[(2-cyanobiphenyl-4-yl)methyl]-2-methoxyimino-4-oxooctanoate (Example 4, Step B) was reacted with 2,6-dichlorophenylhydrazine hydrochloride according to the procedure of Example 4, Step C, to give a 74% yield of the title compound as a light orange gum; homogeneous by TLC in 4:1 hexane-EtOAc. 400 MHz ^{1}H NMR ($CDCl_3$): δ (ppm) 0.84 (t, 3H), 1.00 (t, 3H), 1.31 (m, 2H), 1.56 (m, 2H), 2.62 (t, 2H), 4.10 (q, 2H), 4.26 (s, 2H), 7.2-7.5 (m, 9H), 7.61 (dd, 1H), 7.74 (d, 1H). FAB-MS: m/e 532 $(M+H)^+$.
Analysis ($C_{30}H_{27}Cl_2N_3O_2$)
Calcd: C, 67.67; H, 5.11; N, 7.89
Found: C, 67.38; H, 5.10; N, 7.81

B: Ethyl 3-Butyl-1-(2,6-dichlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

Reaction of the product from Step A with trimethyltin azide according to the method of Example

4, Step D, provided a 51% yield of the title compound as a very pale yellow-tan, stiff foam, mp > 80°C (gradual); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 200 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.89, (t, 3H), 1.00 (t, 3H), 1.36 (m, 2H), 1.63 (m, 2H), 2.66 (t, 2H), 4.12 (q, 2H), 4.28 (s, 2H), 7.15-7.6 (m, 10H), 8.26 (d, 1H), FAB-MS: m/e 575 $(M+H)^+$.

Analysis ($C_{30}H_{28}Cl_2N_6O_2$)

Calcd: C, 62.61; H, 4.90; N, 14.61

Found: C, 62.51; H, 4.94; N, 14.34

EXAMPLE 11

3-BUTYL-1-(2,6-DICHLOROPHENYL)-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]METHYL]-1H-PYRAZOLE-5-CARBOXYLIC ACID

Saponification of ethyl 3-butyl-1-(2,6-biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate according to the procedure of Example 5 gave an 87% yield of the title compound as a white powder, mp >130°C (gradual; preliminary softening); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^1H NMR (DMSO-d_6): δ (ppm) 0.77, (t, 3H), 1.21 (m, 2H), 1.41 (m, 2H), 2.46 (t, 2H), 4.14 (s, 2H), 7.00 (d, 2H), 7.08 (d, 2H), 7.5-7.7 (m, 7H), FAB-MS: m/e 547 $(M+H)^+$.

Analysis ($C_{28}H_{24}Cl_2N_6O_2 \bullet 0.4H_2O$)

Calcd: C, 60.63; H, 4.51; N, 15.15

Found: C, 60.92; H, 4.52; N, 14.76

EXAMPLE 12

ETHYL 3-BUTYL-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]METHYL]-1-[2-(TRIFLUOROMETHYL)PHENYL]-1H-PYRAZOLE-5-CARBOXYLATE

A: Ethyl 3-butyl-4-[(2'-cyanobiphenyl-4-yl-methyl]-1-(2-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylate

Reaction of ethyl 3-[(2'-cyanobiphenyl-4-yl)methyl]-2-methoxyimino-4-oxooctanoate (Example 4, Step B) with 2-(trifluoromethyl)phenylhydrazine hydrochloride according to the method of Example 4, Step C, afforded a 48% yield of the title compound as a light orange gum; homogeneous by TLC in 4:1 hexane-EtOAc. 400MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.84, (t, 3H), 0.94 (t, 3H), 1.30 (m, 2H), 1.55 (m, 2H), 2.60 (t, 2H), 4.05 (q, 2H), 4.23 (s, 2H), 7.26 (d, 2H), 7.4-7.8 (m, 10H) FAB-MS: m/e 532 $(M+H)^+$.
Analysis ($C_{31}H_{28}F_3N_3O_2$)
Calcd: C, 70.04; H, 5.31; N, 7.91
Found: C, 70.30; H, 5.21; N, 7.77

B: Ethyl 3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl-methyl]-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylate

The product from Step A was reacted with trimethyltin azide according to the procedure of Example 4, Step D, to give a 66% yield of the title compound as a golden-tan glass, mp >80°C (gradual); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400MHz

^{1}H NMR ($CDCl_3$): δ (ppm) 0.86,0.90 (overlapping t, each 3H), 1.32 (m, 2H), 1.58 (m, 2H), 2.62 (t, 2H), 4.04 (q, 2H), 4.23 (s, 2H), 7.17 (d, 2H), 7.25 (d, 2H), 7.39 (d, 1H), 7.45 (d, 1H), 7.5-7.7 (m, 4H), 7.75 (d, 1H), 8.25 (d, 1H). FAB-MS: m/e 575 $(M+H)^+$.
Analysis ($C_{31}H_{29}F_3N_6O_2$)
Calcd: C, 64.80; H, 5.09; N, 14.63
Found: C, 64.62; H, 4.89; N, 14.43

EXAMPLE 13

3-BUTYL-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]-METHYL]-1-[2-(TRIFLUOROMETHYL)PHENYL]-1H-PYRAZOLE-5-CARBOXYLIC ACID

The title compound was prepared from ethyl 3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylate (Example 12) by use of the procedure of Example 5. This material was obtained in 90% yield as a white powder, mp > 125°C (gradual; preliminary softening); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^{1}H NMR (DMSO-d_6): δ (ppm) 0.76 (t, 3H), 1.19 (m, 2H), 1.39 (m, 2H), 2.43 (t, 2H), 4.12 (s, 2H), 6.99 (d, 2H), 7.08 (d, 2H), 7.5-7.8 (m, 7H), 7.86 (d, 1H), FAB-MS: m/e 547 $(M+H)^+$.
Analysis ($C_{29}H_{25}F_3N_6O_2$)
Calcd: C, 63.73; H, 4.61; N, 15.38
Found: C, 63.47; H, 4.33; N, 15.09

EXAMPLE 14

ETHYL 3-BUTYL-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]-METHYL]-1H-PYRAZOLE-5-CARBOXYLATE

A: Ethyl 3-Butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-1H-pyrazole-5-carboxylate

The title compound was prepared by reaction of ethyl 3-butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-2-methoxyimino-4-oxooctanoate (Example 4, Step B) with hydrazine hydrochloride under the conditions described in Example 4, Step C, except that only 2 equivalents of hydrazine hydrochloride were used. Purification was achieved by column chromatography on silica gel using a gradient of 5-25% EtOAc in hexane to give a 59% yield of the title compound as a light yellow, stiff gum; homogeneous by TLC in 2:1 hexane-EtOAc. 400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.85 (t, 3H), 1.30 (t overlapping m, total 5H), 1.54 (m, 2H), 2.61 (t, 2H), 4.16 (s, 2H), 4.33 (q, 2H), 5.3 (br s, 1H), 7.23 (d, 2H), 7.35-7.5 (m, 4H), 7.60 (dd, 1H), 7.72 (d, 1H). FAB-MS: m/e 388 $(M+H)^+$.

Analysis ($C_{24}H_{25}N_3O_2$)

Calcd: C, 74.39; H, 6.50; N, 10.84.

Found: C, 74.38; H, 6.57; N, 10.68.

B: Ethyl 3-Butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]-1H-pyrazole-5-carboxylate

The product from Step A was reacted with trimethyltin azide according to the procedure of Example 5, Step D, but in the column chromatography the solvent gradient was increased to a maximum of

7.5% MeOH in CH_2Cl_2. The title compound was obtained in 49% yield as a cream-colored, stiff foam, mp>100° (gradual); nearly homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^1H NMR (DMSO-d_6): δ (ppm) 0.79 (t, 3H), 1.1-1.3 (m, 5H), 1.40 (m, 2H), 2.4-2.55 (m, 2H, overlapping residual DMSO peak), 3.98 (s, 2H), 4.18 (br m, 2H), 6.94 (d, 2H), 7.01 (d, 2H), 7.45-7.65 (m, 4H). FAB-MS: m/e 431 $(M+H)^+$.
Analysis ($C_{24}H_{26}N_6O_2$ • 0.05 H_2O • 0.15 CH_2Cl_2)
Calcd: C, 65.30; H, 5.99; N, 18.92.
Found: C, 65.67; H, 6.07; N, 18.59.

EXAMPLE 15

3-BUTYL-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]METHYL]-1H-PYRAZOLE-5-CARBOXYLIC ACID

Saponification of ethyl 3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl] methyl]-1*H*-pyrazole-5-carboxylate (Example 14) according to the procedure of Example 5 furnished the title compound in 93% yield as a cream-colored powder, mp 205.5-207° C. dec.; homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^1H NMR (DMSO-d_6): δ (ppm) 0.78 (t, 3H), 1.18 (m, 2H), 1.39 (m, 2H), 2.43 (t, 2H), 4.00 (s, 2H), 6.94 (d, 2H), 7.03 (d, 2H), 7.45-7.7 (m, 4H). FAB-MS: m/e 403 $(M+H)^+$.
Analysis ($C_{22}H_{22}N_6O_2$ • 0.95 H_2O)
Calcd: C, 62.98; H, 5.74; N, 20.03.
Found: C, 63.34; H, 5.59; N, 19.67.

EXAMPLE 16

ETHYL 3-BUTYL-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]METHYL]-1-(2,2,2-TRIFLUOROETHYL)-1H-PYRAZOLE-5-CARBOXYLATE

A: Ethyl 3-Butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxylate

A suspension of 210 mg (0.5 mmole) of ethyl 3-[(2'-cyanobiphenyl-4-yl)methyl]-2-methoxyimino-4-oxooctanoate (Example 4, Step B) in 2.0 ml of glacial acetic acid was treated with 189 µl (245 mg, 1.5 mmole) of 70% trifluoroethylhydrazine (aqueous), followed by 125 µl (1.5 mmole) of concentrated (12N) hydrochloric acid. The mixture was stirred under N_2 in an oil bath at 105° C. for 23 hours. The resulting solution was cooled and concentrated in vacuo. The residue was partitioned between 20 ml of EtOAc and 20 ml of 0.2 N HCl. The EtOAc phase was washed with 20 ml of H_2O, then dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and evaporated onto 2.0 g. of silica gel. The resulting dry powder was added as a slurry in hexane to the top of a column of silica gel (34 x 2.3 cm) packed in hexane. Elution with 95:5 hexane-EtOAc yielded 85.9 mg (37%) of the title compound as a nearly colorless, viscous oil; homogeneous by TLC in 4:1 hexane-EtOAc. 400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.84 (t, 3H), 1.21 (t, 3H), 1.29 (m, 2H), 1.52 (m, 2H), 2.54 (t, 2H), 4.13 (s, 2H), 4.27 (q, 2H), 5.23 (q, 2H), 7.16 (d, 2H), 7.35-7.5 (m, 4H), 7.60 (dd, 1H), 7.73 (d, 1H). FAB-MS: m/e 470 $(M+H)^+$.

Analysis ($C_{26}H_{26}F_3N_3O_2$)
Calcd: C, 66.51; H, 5.58; N, 8.95.
Found: C, 66.28; H, 5.67; N, 8.67.

B: Ethyl 3-Butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxylate

The product from Step A was reacted with trimethyltin azide according to the procedure of Example 4, Step D, to give a 65% yield of the title compound as a colorless glass, mp > 45°C (gradual); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^1H NMR ($CDCl_3$): δ (ppm) 0.86 (t, 3H), 1.26 (t, 3H), 1,31, (m, 2H), 1.54 (m, 2H), 2.55 (t, 2H), 4.13 (s, 2H), 4.31 (q, 2H), 5.21 (q, 2H), 7.15 (m, 4H), 7.37 (d, 1H), 7.5-7.6 (m, 2H), 8.21 (d, 1H). FAB-MS: m/e 513 $(M+H)^+$.
Analysis ($C_{26}H_{27}F_3N_6O_2$)
Calcd: C, 60.93; H, 5.31; N, 16.40.
Found: C, 60.64; H, 5.45; N, 16.16.

EXAMPLE 17

3-BUTYL-4-[[2'-(5-TETRAZOLYL)BIPHENYL-4-YL]METHYL-1-(2,2,2-TRIFLUOROETHYL)-1*H*-PYRAZOLE-5-CARBOXYLIC ACID

Ethyl 3-butyl-4-[(2'-cyanobiphenyl-4-yl) methyl]-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole-5-carboxylate (Example 16) was saponified according to the procedure of Example 5 to give an 88% yield of the title compound as a white powder, mp >95°C (gradual); homogeneous by TLC in 9:1 CH_2Cl_2-MeOH. 400 MHz ^1H NMR (DMSO-d_6): δ (ppm) 0.77 (t, 3H), 1.19

(m, 2H), 1.37 (m, 2H), 2.40 (t, 2H), 4.04 (s, 2H), 5.36 (q, 2H), 6.99 (ABq, 4H), 7.45-7.7 (m, 4H).
FAB-MS: m/e 485 $(M+H)^+$.
Analysis ($C_{24}H_{23}F_3N_6O_2 \bullet 0.6H_2O$)
Calcd: C, 58.20; H, 4.92; N, 16.97.
Found: C, 58.33; H, 4.77; N, 16.75.

EXAMPLE 18

ETHYL 4-[[2'-(N-BENZOYLSULFAMOYL)BIPHENYL-4-YL]-METHYL]-3-n-BUTYL-1-(2-CHLOROPHENYL)-1H-PYRAZOLE-5-CARBOXYLATE

A: 2-Bromo-N-(tert-butyl)benzenesulfonamide

To a stirred solution of 2-bromobenzenesulfonyl chloride (Lancaster Synthesis) (2.21 g, 8.65 mmol) in chloroform (40 ml) under nitrogen at room temperature was added tert-butylamine (Aldrich) (2.30 ml, 21.9 mmol). The orange solution was stirred at room temperature for 12 hours, then the mixture evaporated to dryness. Flash chromatography (silica gel, 15% ethyl acetate-hexane) afforded the title compound, (2.12 g, 84%) as a white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.50-7.35 (m, 2H), 5.11 (s, 1H), 1.20 (s, 9H).

B: p-Tolyltrimethyltin

p-Tolylmagnesium bromide solution (Aldrich) (1.0M solution in diethyl ether) (53 ml, 0.0530 mol) was added dropwise to trimethyltin chloride (6.92 g, 0.0347 mol) in tetrahydrofuran (50 ml) under nitrogen

at -10°C. The suspension was allowed to warm slowly to room temperature over 3 hours then saturated ammonium chloride solution (10 ml) was added followed by sufficient water to dissolve the precipitate. The solution was extracted three times with diethyl ether-hexane (1:1). The combined organic phase was washed with brine, dried (magnesium sulfate) and the solvents removed in vacuo. Vacuum distillation of the residue afforded a colorless liquid (39-40°C, 0.1 mm Hg) which was further purified by flash chromatography (silica gel, hexane) to give p-tolyltrimethyltin (7.30 g, 82%) as a colorless liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 7.7 Hz, 2H), 7.19 (d, J = 7.7 Hz, 2H), 2.34 (s, 3H), 0.30 (s, 9H).

C: <u>2'-(N-t-Butylsulfamoyl)-4-methylbiphenyl</u>

2-Bromo-N-(tert-butyl)benzenesulfonamide (from Step A) (1.00 g, 3.92 mmol), p-tolyltrimethyltin (from Step B) (1.95 g, 6.67 mmol), bis(triphenylphosphine)palladium(II) chloride (Aldrich) (165 mg, 0.235 mmol) and dimethylformamide (25 ml) were heated with stirring under nitrogen at 90°C for 5 hours. The black suspension was cooled to room temperature, then filtered through a pad of Celite which was washed with tetrahydrofuran. The colorless filtrate was evaporated to dryness, then chromatographed (silica gel, 10% ethyl acetate-hexane) to give the title compound (0.88 g, 74%) as a white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 7.9 Hz, 1H), 7.60-7.37 (m, 4H), 7.36-7.24 (m, 3H), 3.57 (s, 1H), 2.42 (s, 3H), 0.99 (s, 9H).

D: <u>[2'-(N-t-Butylsulfamoyl)biphenyl-4-yl]methyl bromide</u>

N-Bromosuccinimide (387 mg, 2.17 mmol), α,α'-azobis(isobutyronitrile) (catalytic), 2'-(N-t-butylsulfamoyl)-4-methylbiphenyl (from Step C) (550 mg, 1.81 mmol) and carbon tetrachloride (50 ml) were heated with stirring at reflux for 3 hour. After cooling to room temperature the mixture was filtered and the filtrate evaporated to dryness. Flash chromatography (silica gel, initially 10 and then 20% ethyl acetate-hexane) afforded the title compound [699 mg, 77% pure (the remainder of the material was the corresponding dibromo derivative), 97% yield] as a white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, J = 7.5, 1.6 Hz, 1H), 7.68-7.45 (m, 6H), 7.31 (dd, J = 7.5, 1.6 Hz, 1H), 4.55 (s, 2H), 3.52 (s, 1H), 1.00 (s, 9H).

E: <u>Ethyl 3-[[2'-(N-t-Butylsulfamoyl)biphenyl-4-yl]-methyl]-2-methoxyimino-4-oxooctanoate</u>

A mixture of 50 mg (0.218 mM) of ethyl 2-methoxyimino-4-oxooctanoate (Example 4, Step A), 83 mg (0.218 mM) of [2'-(N-t-butylsulfamoyl)biphenyl-4-yl]methyl bromide (Step D), 36 mg (0.262 mM) of freshly pulverized anhydrous potassium carbonate, and 0.6 mL of dry DMF was stirred vigorously for 24 hours at room temperature at which time the starting material was all consumed [TLC (5:1 hexane/EtOAc)]. The mixture was partitioned between 10mL of EtOAc and 10 mL of 0.2N HCl. The EtOAc layer was then washed with 3 X 10 mL H_2O, 1 X 5 mL brine, and dried briefly over anhydrous sodium sulfate. The filtrate,

obtained from filtration over sintered glass, was concentrated to dryness and the resulting residue was flash chromatographed over 20 mL silica gel (column packed using hexane, sample introduced as a solution in CH_2Cl_2) eluting with 20/1 hexane/ethyl acetate, to give 83 mg (71%) of the desired product as an oil, homogeneous by TLC. R_f=0.35 in 5:1 hexane/EtOAc. ^1H NMR (200 MHz, $CDCl_3$, ppm) = δ 0.88 (t, J=7.2 Hz, 3H), 1.00 (s, 9H), 1.31 (m, 5H), 1.52 (m, 2H), 2.32 (t, J=7.0 Hz, 2H), 3.03 (m, 1H), 3.40 (m, 1H), 3.61 (s, 1H), 4.04 (s, 3H), 4.25 (m, 3H), 7.16-7.52 (m, 7H), 8.15 (m, 1H) Mass spectrum: FAB (m/e) 531 $(M+1)^+$

F: Ethyl 3-n-butyl-1-(2-chlorophenyl)-4-[(2'-sulfamoylbiphenyl-4-yl)methyl]-1H-pyrazole-5-carboxylate

A mixture of 95 mg (0.179 mM) of ethyl 3-[[2'-(N-t-butylsulfamoyl)biphenyl-4-yl]methyl]-1-(2-chlorophenyl)-1H-pyrazole-5-carboxylate (Step E), 96 mg (0.538 mM) of 2-chlorophenylhydrazine hydrochloride, 1 ml glacial acetic acid, and 0.5 mL 2-methoxyethanol was heated at 105°C for 20 hours. After cooling to room temperature, volatiles were evaporated and the residue was co-evaporated with toluene 3x and then flash chromatographed over 40 mL silica gel, eluting with 0.5% $MeOH/CH_2Cl_2$ to give 74 mg of desired material as colorless oil, homogeneous on TLC. TLC: R_f=0.35 in 2% $MeOH/CH_2Cl_2$. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.88 (t, J=7.4 Hz, 3H), 0.98 (t, J=7.1 Hz, 3H), 1.31 (m, 2H), 1.57 (m, 2H), 2.61 (t, J=8.3 Hz, 2H), 4.08 (m, 2H), 4.08 (m, 2H), 4.13 (s, br, 2H), 4.23 (s, 2H), 7.24-7.58 (m, 11H), 8.12 (m, 1H). Mass spectrum: FAB (m/e) 552 $(M+1)^+$.

G: Ethyl 4-[[2'-(N-benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-n-butyl-1-(2-chlorophenyl)-1H-pyrazole-5-carboxylate

A solution of 51 mg (0.093 mM) ethyl 3-n-butyl-1-(2-chlorophenyl)-4-[(2'-sulfamoyl-biphenyl-4-yl)methyl]-1H-pyrazole-5-carboxylate (Step F), 140 mg (1.0 mM) of benzoyl chloride, and 1 mL dry pyridine was stirred vigorously under N_2 at room temperature for 36 hours. After 4 hr, a yellow-orange salt fell out of solution. The reaction mixture was partitioned between 4mL aqueous saturated KH_2PO_4 and 5 mL EtOAc. The aqueous layer was extracted further using 2 x 5 mL EtOAc, and the combined organic layers were washed with brine and dried over sodium sulfate. After filtration, solvents were evaporated and the residue was coevaporated with toluene 3x before being loaded on a flash column (15mL SiO_2) and eluted with 0.5-1.0-2.0% $MeOH/CH_2Cl_2$ to give 35 mg of a clear glass (57%) homogeneous on TLC: R_f=0.4 (5% $MeOH/CH_2Cl_2$)
^1H NMR (400 MHz, $CDCl_3$, ppm) δ 0.87 (t, J=7.3 Hz, 3H), 0.96 (t, J=7.1 Hz, 3H), 1.33 (m, 2H), 1.58 (m, 2H), 2.58 (t, J=8.0 Hz, 3H), 4.08 (m, 2H), 4.15 (s, 2H), 7.03-7.64 (m, 15H), 8.08 (m, 1H), 8.36(m, 1H)
Mass spectrum: FAB (m/e) 656 $(M+1)^+$

EXAMPLE 19

4-[[2'-(N-BENZOYLSULFAMOYL)BIPHENYL-4-YL]METHYL]-3-n-BUTYL-1-(2-CHLOROPHENYL)-1H-PYRAZOLE-5-CARBOXYLIC ACID

A solution of 24 mg (0.0366 mM) ethyl 4-[2'-(N-benzoylsulfamoyl)biphenyl-4-yl]methyl]-3-n-butyl-1-(2-chlorophenyl)-1H-pyrazole-5-carboxylate (Example 18), 146 µL of a 2.5N NaOH solution (0.366 mM), and 300 µL methanol was stirred at 60°C for 2h. After filtration, the volatiles were evaporated under reduced pressure and the residue acidified with 1N HCl/MeOH solution (500 µL) to pH ~1.5. After the volatiles were evaporated, the residue was triturated with chloroform and filtered. The residue obtained after evaporation of the volatiles was pumped overnight to give 21 mg off-white solid (91%), homogeneous by TLC R_f=0.3 (10% MeOH/CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.87 (t, J=7.4 Hz, 3H), 1.34 (m, 2H), 1.60 (m, 2H), 2.60 (t, J=8.0 Hz, 2H), 4.11 (s, 2H) 7.03-7.63 (m, 15H), 8.36-8.41 (m, 2H) Mass spectrum: FAB (m/e):628 $(M+1)^+$
Analysis ($C_{34}H_{30}ClN_3O_5S$•1.1 H_2O)
Calc'd = C, 63.02; H, 5.00; N, 6.48
Found = C, 62.75; H, 4.67; N, 6.54

EXAMPLE 20

3-n-BUTYL-1-(2-CHLOROPHENYL)-4-[2'-[N-(TRIFLUORO-ACETYL)SULFAMOYL]BIPHENYL-4-YL]METHYL]-1H-PYRAZOLE-5-CARBOXYLIC ACID.

A: <u>Ethyl 3-n-butyl-1-(2-chlorophenyl)-4-[[N-(trifluoroacetyl)sulfamoyl]biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate</u>

A solution of 74 mg (0.134 mM) ethyl 3-n-butyl-1-(2-chlorophenyl)-4-[(2'-sulfamoylbiphenyl-4-yl)methyl]-1H-pyrazole-5-carboxylate (Example 18, Step F), 281 mg (1.34 mM) trifluoroacetic anhydride, and 1.3 mL dry pyridine was vigorously stirred at room temperature for 24 h. The resulting brown solution was partitioned between 3 mL saturated aqueous KH_2PO_4 and 3 mL ethyl acetate. The aqueous layer was further extracted with 2 x 3 mL EtOAc, and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration, volatiles were evaporated and the residue was flash chromatographed over 15 mL silica gel using gradient elution (2-10% MeOH/CH_2Cl_2) to give 26 mg of the desired product in its K^+ salt form as indicated by MS (FAB). The material was acidified with 1 mL 1N aq HCl and extracted with 2 x 1 mL CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and filtered. Solvents were evaporated to give 17 mg of the desired compound as a glassy solid.

TLC: R_f=0.4 (10% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.78 (m, 6H), 1.29 (m, 2H), 1.55 (m, 2H), 2.56 (t, J=7.6 Hz, 2H), 3.97 (m, 2H), 4.09 (s, 2H), 7.05-7.60 (m, 11H), 8.13 (m, 1H)

Mass spectrum: FAB (m/e):648 $(M+1)^+$

B: 3-n-Butyl-1-(2-chlorophenyl)-4-[(2'-sulfamoyl-biphenyl-4-yl)methyl]-1H-pyrazole-5-carboxylic acid

A solution of 17 mg (0.026 mM) of ethyl 3-n-butyl-1-(2-chlorophenyl)-4-[N-(trifluoroacetyl)-sulfamoyl]biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate (Step A), 104 µL of 2.5 N aq NaOH solution, and 200 µL of MeOH was stirred at 60°C for 2 h. After filtration volatiles were evaporated, and the residue was acidified to pH 1.5 using 1N HCl/MeOH. Volatiles were again evaporated and the residue was flash chromatographed over 10 mL silica gel eluting with 2-5-10% MeOH/CH_2Cl_2, to give 11 mg of a gum, NMR and MS consistent with the title compound; TLC R_f=0.1 (10% MeOH/CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.84 (t, J=7.4 Hz, 3H), 1.30 (m, 2H), 1.55 (m, 2H), 2.59 (t, J=7.8 Hz, 2H), 4.20 (s, 4H), 7.22-7.58 (m, 11H), 8.10 (m, 1H)
Mass spectrum: FAB (m/e): 524 $(M+1)^+$

C: 3-n-Butyl-1-(2-chlorophenyl)-4-[[2'-[N-(trifluoro-acetyl)sulfamoyl]biphenyl-4-yl]methyl]-1H-pyra-zole-5-carboxylic acid

A solution of 9.3 mg (0.0178 mM) 3-n-butyl-1-(2-chlorophenyl)-4-[(2'-sulfamoylbiphenyl-4-yl)-methyl]-1H-pyrazole-5-carboxylic acid (Step B), 0.2 mL dry pyridine, and 37 mg (0.178 mM) trifluoroacetic anhydride was stirred at room temperature for 24 hr. The resulting mixture was partitioned between 1 mL sat. aq. KH_2PO_4 and 2mL ethyl acetate. The aqueous layer was further extracted with 2 mL EtOAc, and the combined organic layers were washed with brine and

dried over anhydrous Na_2SO_4. After filtration, the volatiles were removed and the residue was flash chromatographed over 10 mL silica gel, eluting with 2-10% $MeOH/CH_2Cl_2$ to give 9.3 mg single spot material as an off white solid. This material was mainly the potassium salt of the desired product, as shown by MS (FAB). Therefore, it was acidified using 1 mL 1N aq HCl and extracted with 2x1 mL CH_2Cl_2, and dried using Na_2SO_4. After filtration, volatiles were evaporated to give 5.3 mg of off-white foam. TLC:R_f = 0.3 (10% $MeOH/CH_2Cl_2$)

^1H NMR (400 MHz, CD_3OD, ppm) δ 0.88 (t, J=7.3 Hz, 3H), 1.33 (m, 2t), 1.54 (m,2H), 2.61 (t, J=7.6 Hz, 2H), 4.24 (s, 2H), 7.15-7.57 (m, 11H), 8.14 (m, 2H).
Mass spectrum: FAB (m/e): 620 $(M+1)^+$

EXAMPLE 21

3-n-BUTYL-1-(2-CHLOROPHENYL)-4-[(2'-[N-(TRIFLUOROMETHANESULFONYL)AMINO]BIPHENYL-4-YL]METHYL]-1H-PYRAZOLE-5-CARBOXYLIC ACID

A: 4-Methyl-2'-nitrobiphenyl

Under N_2, a clean, dry flask was charged with p-tolyltrimethyltin (Example 18, Step B) (5.61 g, 0.022 mol), 2-bromonitrobenzene (4.04 g, 0.020 mol), anhydrous DMF (40 mL), and palladium(II) bis(triphenylphosphine)dichloride (140 mg, 0.2 mmol), heated at 110°C and stirred for 4 h when TLC (4:1 hexane/EtOAc) indicated disappearance of starting materials. The nearly black reaction mixture was cooled to room temperature, poured into a solution

made from 100 mL 1N KOH and 100 mL sat. NaCl, and extracted with 3 x 150 mL EtOAc. The combined organic layers were washed with 100 mL 1N KOH and 100 mL sat. NaCl, and then dried over anhydrous Na_2SO_4. After filtration, the amber solution was evaporated to dryness and then flash chromatographed over 900 mL SiO_2, eluting with 2.5% EtOAc-hexane to give 4.109 g (96%) of the title compound as a light orange liquid, homogeneous on TLC (4/1 hex-EtOAc).

^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 2.38 (s, 3H), 7.21 (m, 4H), 7.43 (m, 2H), 7.58 (m, 1H), 7.80 (dd, J=8.09, 1.34 Hz, 1H).

Mass spectrum:El (m/e):213 (M^+)

B: <u>(2'-Nitrobiphenyl-4-yl)methyl bromide</u>

4-Methyl-2'-nitrobiphenyl (Step A) (2.173 g, 10.2 mmol) was dissolved in CCl_4 (100 mL) and heated to reflux with stirring . To this was added a bromine solution [prepared by diluting 11.2 ml (11.2 mmole) of commercial 1.0 M solution in CCl_4 to a final volume of 40 mL with CCl_4] dropwise while a 100 W lamp was used to irradiate the refluxing reaction mixture. After completion of addition, the solution was cooled to room temperature, volatiles were removed, and the residue was flash chromatographed over 700 mL SiO_2, eluting with 1.5-4.0-10.0% EtOAc/hexane, to afford 2.68 g (90%) of the title compound, 85% pure as indicated by NMR (the remainder being the dibrominated material), but homogeneous on TLC (4/1 hex-EtOAc).

^1H NMR (400 MHz, $CDCl_3$, ppm) δ 4.52 (s, 2H), 7.29 (m, 2H), 7.48 (m, 4H), 7.61 (m, 1H), 7.85 (dd, J=8.05, 1.26 Hz, 1H). Mass spectrum: FAB (m/e): 292 $(M+1)^+$

C: <u>Ethyl 2-methoxyimino-3-[(2'-nitrobiphenyl-4-yl)methyl]-4-oxooctanoate</u>

A mixture of 650 mg (2.84 mM) of ethyl 2-methoxyimino-4-oxooctanoate (Example 4, Step A), 829 mg (2.84 mM) of (2'-nitrobiphenyl-4-yl)methyl bromide (from Step B), 470 mg (3.41 mM) of freshly pulverized anhydrous potassium carbonate, and 9 mL of dry DMF, was stirred vigorously under nitrogen at room temperature for 16 hours. The resulting mixture was partitioned between 90 mL 0.2N HCl and 90 mL EtOAc. The aqueous layer was further extracted with 30 mL EtOAc and the combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. After filtration, the volatiles were removed to give a crude product mixture which was flash chromatographed over 300 mL silica gel, eluting with 20/1 to 10/1 hexane/ethyl acetate, to afford 940 mg (75%) of a colorless oil, homogeneous on TLC. TLC: R_f=0.3 (4/1 hex/EtOAc).
^1H NMR (400 MHz, $CDCl_3$, ppm): δ 0.86 (t, J=7.3 Hz, 3H), 1.25 (m, 5H), 1.53 (m, 2H), 2.31 (m, 2H), 2.96 (m, 1H), 3.40 (m, 1H), 3.98 (s, 3H), 4.24 (m, 2H), 7.16-7.81 (m, 8H). Mass spectrum (m/e) 441 $(M+1)^+$.

D: Ethyl 3-n-butyl-1-(2-chlorophenyl)-4-[(2'-nitrobiphenyl-4-yl)methyl]-1H-pyrazole-5-carboxylate

A mixture of 381 mg (0.866 mM) of ethyl 2-methoxyimino-3-[(2'-nitrobiphenyl-4-yl)methyl]-4-oxooctanoate (Step C), 465 mg (2.60 mM) of 2-chlorophenylhydrazine hydrochloride, 4.4 mL glacial acetic acid and 2.2 mL 2-methoxyethanol was heated with vigorous stirring at 105°C for 24 hours. After cooling to room temperature, volatiles were evaporated and the residue was coevaporated with toluene 3X before being flash chromatographed over 120 mL silica gel, eluting with 15/1 hexane/ethyl acetate, to give 274 mg (62%) of a yellow oil, homogeneous on TLC. TLC: R_f=0.45 (4/1 hexane/ethyl acetate).
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 0.85 (t, J=7.4 Hz, 3H), 0.99 (t, J=7.1 Hz, 3H), 1.31 (m, 2H), 1.55 (m, 2H), 2.60 (m, 2H), 4.09 (m, 2H), 4.21 (s, 2H), 7.21-7.82 (m, 12H). Mass spectrum: FAB (m/e) 518 $(M+1)^+$.

E: Ethyl 4-[(2'-aminobiphenyl-4-yl)methyl]-3-n-butyl-1-(2-chlorophenyl)-1H-pyrazole-5-carboxylate

A mixture of 42 mg (0.081 mM) of ethyl 3-n-butyl-1-(2-chlorophenyl)-4-[(2'-nitrobiphenyl-4-yl)-methyl]-1H-pyrazole-5-carboxylate (Step D), 4.5 mg of platinum oxide, and 2 mL ethyl acetate was hydrogenated under a H_2-balloon at room temperature for 30 minutes. The catalyst was removed by filtering over a pad of Celite, the filtrate was

pumped to dryness, and then flash chromatographed over 10 mL silica gel using 15/1->10/1 hexane/ethyl acetate to give 33 mg (33%) of a yellow oil, homogeneous on TLC. TLC:R_f=0.35 (4/1 hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 0.84 (m, 3H), 0.99 (m, 3H), 1.32 (m, 2H), 1.56 (m, 2H), 2.60 (t, J=7.7 Hz, 2H), 4.11 (m, 2H), 4.19 (s, 2H), 6.84-7.47 (m, 12H). Mass spectrum: FAB (m/e) 488 $(M+1)^+$.

F: Ethyl 4-[[2'-[N,N-bis(trifluoromethanesulfonyl)amino]biphenyl-4-yl]methyl]-3-n-butyl-1-(2-chlorophenyl)-1H-pyrazole-5-carboxylate

A mixture of 30 mg (0.062 mM) of ethyl 4-[(2'-aminobiphenyl-4-yl)methyl]-3-n-butyl-1-(2-chlorophenyl)-1H-pyrazole-5-carboxylate (Step E), 175 mg (0.62 mM) of trifluoromethanesulfonic anhydride, and 0.6 mL anhydrous pyridine was stirred at room temperature, under N_2, for 6 hours. The dark red reaction mixture was treated with 2 mL 1N HCl, 2 mL saturated aqueous KH_2PO_4 and extracted with 2 x 4 mL EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration, volatiles were evaporated and the residue was coevaporated 3x with toluene before being flash chromatographed over 15 mL of silica gel, eluting with 20/1 hexane/ethyl acetate to give 20 mg of a hard gum, homogeneous by TLC.

^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 0.88 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H), 1.33 (m, 2H), 1.58 (m, 2H), 2.62 (t, J=7.6 Hz, 2H), 4.10 (m, 2H), 4.25 (s, 2H), 7.23-7.61 (m, 12H).

Mass spectrum:FAB (m/e) 751 $(M+1)^+$

G: 3-n-Butyl-1-(2-chlorophenyl)-4-[[2'-[N-(trifluoromethanesulfonyl)amino]biphenyl-4-yl]-methyl]-1H-pyrazole-5-carboxylic acid

A solution of 20 mg (0.027 mM) of ethyl 4-[[2'-[N,N-bis(trifluoromethanesulfonyl)amino]biphenyl-4-yl]methyl]-3-n-butyl-1-(2-chlorophenyl)-1H-pyrazole-5-carboxylate (Step F), 104 µL of 2.5N NaOH, and 200 µL MeOH was stirred at room temperature for 4 hours. Volatiles were evaporated and the residue was acidified using 1 mL 2N HCl and extracted with 2 x 1 mL CH_2Cl_2. Combined CH_2Cl_2 layers were dried over anhydrous Na_2SO_4. After filtration, solvents were removed to give an off white solid, single spot by TLC. TLC:R_f=0.15 (10% MeOH/CH_2Cl_2).
^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 0.86 (t, J=7.3 Hz, 3H), 1.32 (m, 2H), 1.58 (m, 2H), 2.61 (t, J=7.6 Hz, 2H), 4.25 (s, 2H), 6.74 (s, 1H), 7.19-7.64 (m, 12H).
Mass spectrum:FAB (m/e) 592 $(M+1)^+$

EXAMPLE 22

3-BUTYL-1-(2-CHLOROPHENYL)-5-(TRIFLUOROMETHANESULFONAMIDO)-4-[(2'-TETRAZOL-5-YL)BIPHENYL-4-YL]METHYL]-PYRAZOLE

A: 5-Amino-3-Butyl-1-(2-chlorophenyl)-4-[(2'-(N(2)-(triphenylmethyl)tetrazol-5-yl)biphen-4-yl)methyl]pyrazole

To a solution of 408.5 mg (0.838 mmol) 5-amino-3-butyl-1-(2'-chlorophenyl)-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole (Example 2) in 10 mL CH_2Cl_2 were added 0.292 mL (2.10 mmol) triethylamine

and 234 mg (2.10 mmol) chlorotriphenylmethane. After four hours, the mixture was poured into brine and extracted 3 times with ether. The combined organic material was washed with brine, dried over $MgSO_4$, stripped of solvent <u>in vacuo</u>, then was medium pressure chromatographed on silica gel using 30% EtOAc/hexane to give 327.1 mg of title compound, 54% yield. R_f 0.16 in 30% EtOAc/hexane, visualized by UV and ammonium molybdate/ceric sulfate stain; ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (m, 1H), 7.53-7.14 (m, 17H), 7.05 (4 line me, 4H), 6.91 (m, 5H), 3.67 (s, 2H), 3.02 (br s, 2H), 2.54 (3 line m, 2H), 1.63 (m, 2H), 1.36 (6 line m, 2H), 0.89 (3 line m, 3H).

B: <u>3-Butyl-1-(2-chlorophenyl)-5-(trifluoro methanesulfonamido)-4-[(2'-(N(2)-(triphenylmethyl)tetrazol-5-yl)biphen-4-yl)-methyl]pyrazole</u>

To a solution of 217 mg (0.299 mmol) 5-amino-3-butyl-1-(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]pyrazole and 0.295 mL (2.23 mmol) 2,4,6-collidine in 5 mL CH_2Cl_2 was added 0.201 mL trifluoromethanesulfonic anhydride. After 1 hour, the mixture was poured into brine and extracted 3 times with ether. The combined organic material was washed with brine, dried over $MgSO_4$, stripped of solvent <u>in vacuo</u>, then was medium pressure chromatographed on silica gel using 15% EtOAc/hexane to give title compound. R_f 0.54 in 35% EtOAc/hexane, visualized by UV and ammonium molybdate/ceric sulfate stain;

^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (m, 1H), 7.78 (m, 1H), 7.49 (m, 5H), 7.40-7.21 (m, 11H), 7.05 (4 line m, 4H), 6.95 (m, 5H), 3.81 (benzylic CH_2, AB, J=15.7 Hz, Δυ-16.0 Hz, 2H), 2.81 (m, 2H), 1.65 (m, 2H), 1.30 (m, 2H), 0.85 (3 line m, 3H).

C: 3-Butyl-1-(2-chlorophenyl)-5-(trifluoro methanesulfonamido)-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole

To a solution of the trityl protected title compound in 10 mL methanol was added 10 drops concentrated HCl. After 30 minutes, an indicator quantity of phenolphthalein was added and the mixture was basified with 10% NaOH then reacidified with HOAc. Ether and brine were added and the mixture extracted 3 times with ether. The combined organic material was dried over $MgSO_4$, stripped of solvent *in vacuo*, then was medium pressure chromatographed on silica gel using 1/50/49 AcOH/EtOAc/hexane. The title compound was obtained in pure form after being HPLC'd using the following conditions: Rainin Dynamax® C-18 column, 25 x 2.14 cm w/Guard Column; gradient of acetonitrile in water 5 to 100% over 60 minutes at 5 mL/minute; R_f 0.23 in 1/65/34 AcOH/EtOAc/ hexane, visualized by UV and ammonium molybdate/ceric sulfate stain;
^1H NMR (300 MHz, CD_3OD): δ 7.71-7.43 (3 overlapping m, 8H), 7.12 (4 line m, 4H), 3.90 (s, 2H), 2.39 (3 line m, 2H), 1.46 (m, 2H), 1.27 (m, 2H), 0.85 (3 line m, 3H); MS (FAB) m/e 616 (M+1).

EXAMPLE 23

Typical Pharmaceutical Compositions Containing a Compound of the Invention

A: Dry Filled Capsules Containing 50 mg of Active Ingredient Per Capsule

Ingredient	Amount per capsule (mg)
3-butyl-1-(2-chlorophenyl)-4-[[2'-(5-tetrazolyl)-biphenyl-4-yl]methyl-1H-pyrazole-5-carboxylic acid	50
Lactose	149
Magnesium stearate	1
Capsule (size No. 1)	200

The 3-butyl-1-(2'-chlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl-1H-pyrazole-5-carboxylic acid can be reduced to a No. 60 powder and the lactose and magnesium stearate can then be passed through a No. 60 blotting cloth onto the powder. The combined ingredients can then be mixed for about 10 minutes and filled into a No. 1 dry gelatin capsule.

B: Tablet

A typical tablet would contain 3-butyl-1-(2-chlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl-1H-pyrazole-5-carboxylic acid (25 mg), pregelatinized starch USP (82 mg), microcrystalline cellulose (82 mg) and magnesium stearate (1 mg).

C: Combination Tablet

A typical combination tablet would contain, for example, 3-butyl-1-(2-chlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl-1H-pyrazole-5-carboxylic acid, a diuretic such as hydrochlorothiazide and consist of hydrochlorothiazide (50 mg) pregelatinized starch USP (82 mg), microcrystalline cellulose (82 mg) and magnesium stearate (1 mg).

D: Suppository

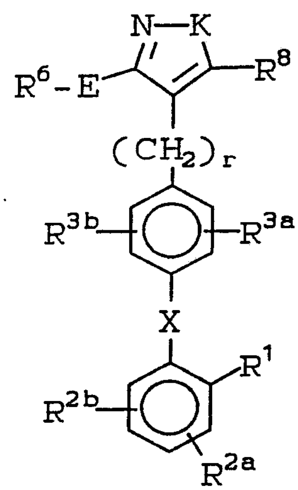
Typical suppository formulations for rectal administration can contain 3-butyl-1-(2-chlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl-1H-pyrazole-5-carboxylic acid, (0.08-1.0 mg), disodium calcium edetate (0.25-0.5 mg), and polyethylene glycol (775-1600 mg). Other suppository formulations can be made by substituting, for example, butylated hydroxytoluene (0.04-0.08 mg) for the disodium calcium edetate and a hydrogenated vegetable oil (675-1400 mg) such as Suppocire L, Wecobee FS, Wecobee M, Witepsols, and the like, for the polyethylene glycol. Further, these suppository formulations can also include another active ingredient such as another antihypertensive and/or a diuretic and/or an angiotensin converting enzyme and/or a calcium channel blocker in pharmaceutically effective amounts as described, for example, in C above.

E: Injection

A typical injectible formulation would contain 3-butyl-1-(2-chlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl-1H-pyrazole-5-carboxylic acid, sodium phosphate dibasic anhydrous (11.4 mg), benzyl alcohol (0.01 ml) and water for injection (1.0 ml). Such an injectible formulation can also include a pharmaceutically effective amount of another active ingredient such as another antihypertensive and/or a diuretic and/or an angiotensin converting enzyme inhibitor and/or a calcium channel blocker.

WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

or a pharmaceutically acceptable salt thereof wherein:

K is O, S, or NR^7;

R^1 is (a) $-CO_2R^5$,

(b) $-SO_3R^5$,

(c) $-NHSO_2(C_1-C_4\text{-polyfluoroalkyl})$,

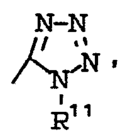
(d) $-PO(OR^5)_2$,

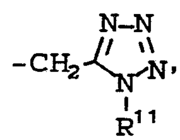
(e) $-SO_2-NH-R^9$,

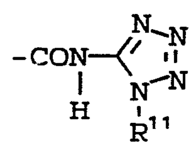
(f) $-CONHOR^5$,

(g) $-\overset{\displaystyle OH}{\underset{\displaystyle R^9}{C}}-\overset{\displaystyle O}{\underset{\displaystyle OR^5}{\overset{\|}{P}}}-OR^5$,

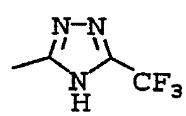
(h)-SO_2NH-heteroaryl,
(i)-CH_2SO_2NH-heteroaryl,
(j)-SO_2NH-CO-R^{23},
(k)-CH_2SO_2NH-CO-R^{23},
(l)-CONH-SO_2R^{23},
(m)-CH_2CONH-SO_2R^{23},
(n)-$NHSO_2NHCO$-R^{23},
(o)-$NHCONHSO_2$-R^{23},

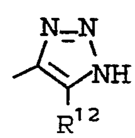
(p) 

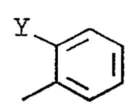
(q) 

(r) 

(s) -$CONHNHSO_2CF_3$,

(t) 

(u) 

(v) 

wherein Y is

(1) $-CO_2R^4$,

(2) $-SO_3R^5$,

(3) $-NHSO_2CF^3$,

(4) $-PO(OR^5)_2$,

(5) $-SO_2NHR^9$,

(6) 1H-tetrazol-5-yl.

(w) $-\overset{\overset{O}{\|}}{\underset{\underset{OR^5}{|}}{P}}-R^{23}$, or

(x) $NH\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{\underset{\underset{OR^5}{\backslash}}{P}}-R^{23}$;

wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted five or six membered aromatic ring comprising from 1 to 3 heteroatoms selected from the group consisting of O, N and S and wherein the substituents are members selected from the group consisting of -OH, -SH, $-C_1-C_4$-alkyl, $-C_1-C_4$-alkoxy, $-CF_3$, halo, $-NO_2$, $-CO_2H$, $-CO_2-C_1-C_4$-alkyl, $-NH_2$, $NH(C_1-C_4$-alkyl), $-N(C_1-C_4$-alkyl$)_2$ and a fused benzo group;

R^{2a} and R^{2b} are independently

(a) H,

(b) halo,

(c) NO_2,

(d) NH_2,

(e) C_1-C_4-alkylamino,

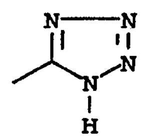
(f) di-(C_1-C_4-alkyl)amino

(g) SO_2NHR^9,
(h) CF_3,
(i) C_1-C_4-alkyl, or
(j) C_1-C_4-alkoxy;

R^{3a} is
(a) H,
(b) halo,
(c) C_1-C_6-alkyl,
(d) C_1-C_6-alkoxy, or
(e) C_1-C_6-alkoxy-C_1-C_4-alkyl;

R^{3b} is
(a) H,
(b) halo,
(c) NO_2,
(d) C_1-C_6-alkyl,
(e) C_2-C_6-alkanoyloxy,
(f) C_3-C_6-cycloalkyl,
(g) C_1-C_6-alkoxy,
(h) $-NHSO_2R^4$,
(i) hydroxy-C_1-C_4-alkyl,
(j) aryl-C_1-C_4-alkyl,
(k) C_1-C_4-alkylthio,
(l) C_1-C_4-alkylsulfinyl,
(m) C_1-C_4-alkylsulfonyl,
(n) NH_2,
(o) C_1-C_4-alkylamino,
(p) di(C_1-C_4-alkyl)amino,
(q) CF_3,
(r) $-SO_2$-NHR^9,
(s) aryl or
(t) furyl;

wherein aryl is phenyl or naphthyl either unsubstituted or substituted with one, two or three substituents selected from the group consisting of halo, C_1-C_4-alkyl, C_1-C_4-alkoxy, NO_2, CF_3, C_1-C_4-alkylthio, OH, NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -CO_2H, -CO_2-C_1-C_4-alkyl, C_1-C_4-polyfluoroalkyl, C_3-C_6-polyfluorocycloalkyl, and



;

R^4 is H, C_1-C_6-alkyl, aryl or -CH_2-aryl;

R^5 is H, $-\overset{R^4}{\overset{|}{C}}H-O-\overset{O}{\overset{\|}{C}}-R^{4a}$, wherein R^{4a} is C_1-C_6-alkyl, aryl, or -CH_2-aryl;

E is a single bond, -$NR^{13}(CH_2)_s$-, -$S(O)_x(CH_2)_s$- where x is 0 to 2 and s is 0 to 5, -CH(OH)-, -O-, -CO-;

R^6 is

C_1-C_6-alkyl, C_2-C_5-alkenyl or C_2-C_5-alkynyl each of which can be substituted with a substituent selected from the group consisting of aryl, C_3-C_7-cycloalkyl, halo, -OH, -CF_3, -CCl_3, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -NH-SO_2R^4, -$COOR^4$, -SO_2NHR^9, C_1-C_4-alkoxy, or C_1-C_4-alkyl-S;

R^7 is

(a) -H,

(b) C_1-C_{10}-alkyl;

(c) substituted C_1-C_{10}-alkyl in which one or more substituent(s) is selected from

(1) I, Br, Cl, or F,

(2) hydroxy,

(3) C_1-C_{10}-alkoxy,

(4) C_1-C_5-alkoxycarbonyl,

(5) C_1-C_4-alkylcarbonyloxy,

(6) C_3-C_8-cycloalkyl,

(7) aryl,

(8) heteroaryl,

(9) C_1-C_{10}-alkyl-$S(O)_p$ in which p is 0 to 2,

(10) C_3-C_8-cycloalkyl-$S(O)_p$,

(11) aryl-$S(O)_p$,

(12) oxo,

(13) carboxy,

(14) NR^9R^9,

(15) C_1-C_5-alkylaminocarbonyl,

(16) di(C_1-C_5-alkyl)aminocarbonyl,

(17) cyano;

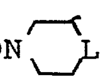
(18) $-OCONR^{22}R^{23}$

(19) $NR^{22}COR^{23}$

(20) $-NR^{22}CO_2R^{23}$

(21) $-NR^{22}CONR^{22}R^{23}$

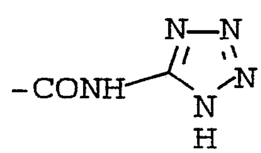
(22) $-NR^{22}CON$  L

(23) -OCON  L wherein L is a single bond, CH_2, O, $S(O)_p$ or NR^9

(d) C_2-C_{10}-alkenyl,
(e) C_2-C_{10}-alkynyl,
(f) C_3-C_8-cycloalkyl,
(g) substituted C_3-C_8-cycloalkyl or substituted C_3-C_8-cycloalkyl-C_1-C_4-alkyl having one or more substituents selected from the group:
    (1) Cl, Br, F, or I
    (2) hydroxy,
    (3) C_1-C_6-alkyl,
    (4) C_1-C_6-alkoxy,
    (5) C_1-C_4-alkylcarbonyloxy,
    (6) C_1-C_5-alkoxycarbonyl,
    (7) carboxy,
    (8) oxo,
    (9) C_1-C_5-alkylaminocarbonyl,
    (10) di(C_1-C_5-alkyl)aminocarbonyl,
    (11) C_1-C_4-alkylcarbonyl, and
    (12) aryl,
(h) aryl, or
(i) heteroaryl;

R^8 is (a) hydrogen,
(b) -OH,
(c) $-NH_2$,
(d) -NH(C_1-C_4-alkyl) wherein the alkyl is unsubstituted or substituted with CO_2R^4,
(e) -N(C_1-C_4-alkyl)$_2$ wherein one or both of the alkyl groups can be substituted with CO_2R^4,
(f) $-NHCO_2$-C_1-C_4-alkyl,
(g) $-NHSO_2$-aryl,
(h) $-NHSO_2$-heteroaryl
(i) $-NHSO_2$(C_1-C_4-polyfluoroalkyl),

(j) $-CO_2H$,
(k) $-CO_2R^5$,
(l) halo,
(m) $-CONHSO_2$-aryl,
(n) $-CONHSO_2$-heteroaryl,
(o) $-CONHSO_2-C_1-C_4$-alkyl, either unsubstituted or substituted with aryl, $-NH_2$, $-NH(C_1-C_4$-alkyl), $-N(C_1-C_4$-alkyl$)_2$; -OH, $-CO_2H$, or $CO_2(C_1-C_4$-alkyl),
(p) $-CONHSO_2(C_1-C_4$-polyfluoroalkyl),
(q) $-CH_2OH$,
(r) $-CH_2OCOR^4$,
(s) $-O-C_1-C_4$-alkyl,
(t) $-S(O)_x-C_1-C_4$-alkyl, either unsubstituted or substituted with aryl, $-NH_2$, $-NH(C_1-C_4$-alkyl), $-N(C_1-C_4$-alkyl)2, -OH, $-CO_2H$, or $CO_2(C_1-C_4$-alkyl),
(u) $-SO_2NHR^{21}$,
(v) -CN,
(w) tetrazol-5-yl,

(x)  ,

(y) $-CH_2CO_2R^4$;

R^9 is H, C_1-C_5-alkyl, aryl or $-CH_2$-aryl;
R^{10} is H, C_1-C_4-alkyl;
R^{11} is H, C_1-C_6-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy alkyl, or $-CH_2-C_6H_4R^{20}$;

R^{12} is -CN, $-NO_2$, $-CO_2R^4$, or $-CF_3$;

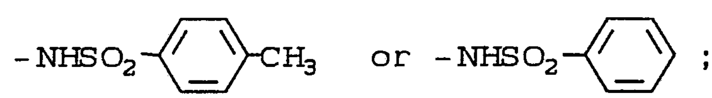
R^{13} is H, C_2-C_4-alkanoyl, C_1-C_6-alkyl, allyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{14} is H, C_1-C_8-alkyl, C_1-C_8-perfluoroalkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{15} is H, C_1-C_6-alkyl;

R^{16} is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{17} is $-NR^9R^{10}$, $-OR^{10}$, $-NHCONH_2$, $-NHCSNH_2$,



R^{18} and R^{19} are independently C_1-C_4-alkyl or taken together are $-(CH_2)_q-$ where q is 2 or 3;

R^{20} is H, $-NO_2$, $-NH_2$, -OH or $-OCH_3$;

R^{21} is
(a) -CO-aryl,
(b) -CO-C_1-C_4-alkyl,
(c) $-COCF_3$,
(d) -CO-heteroaryl, or
(e) heteroaryl;

R^{23} is
(a) aryl,
(b) heteroaryl,
(c) C_3-C_7-cycloalkyl,
(d) C_1-C_6-alkyl either unsubstituted or substituted with aryl, heteroaryl, -OH, -SH, C_1-C_4-alkyl, C_3-C_7-cycloalkyl, $-O(C_1$-C_4-alkyl),

$-S(C_1-C_4\text{-alkyl})$, $-CF_3$, halo, $-NO_2$, $-CO_2H$, $CO_2-C_1-C_4\text{-alkyl}$, $-NH_2$, NHaryl, $N(\text{aryl})_2$, $-NH(C_1-C_4\text{-alkyl})$, $-N(C_1-C_4\text{-alkyl})_2$, $-PO_3H$, $-PO(OH)(O-C_1-C_4\text{-alkyl})$, or $-N(CH_2CH_2)_2L$ wherein L is single bond, $-CH_2-$, $-O-$, $-S(O)p$, or NR^9; and

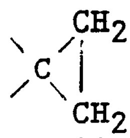
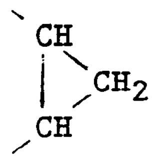
(e) polyfluoro-C_1-C_4-alkyl;

X is

(a) a carbon-carbon single bond,
(b) $-CO-$,
(c) $-O-$,
(d) $-S-$,
(e) $-\underset{\textstyle R^{13}}{\underset{|}{N}}-$,
(f) $-CO\underset{\textstyle R^{15}}{\underset{|}{N}}-$,
(g) $-\underset{\textstyle R^{15}}{\underset{|}{N}}CO-$,
(h) $-OCH_2-$,
(i) $-CH_2O-$
(j) $-SCH_2-$,
(k) $-CH_2S-$,
(l) $-NHC(R^9)(R^{10})$,
(m) $-NR^9SO_2-$,
(n) $-SO_2NR^9-$,
(o) $-C(R^9)(R^{10})NH-$,
(p) $-CH=CH-$,
(q) $-CF=CF-$,
(r) $-CH=CF-$,
(s) $-CF=CH-$,

(t) $-CH_2CH_2-$,

(u) $-CF_2CF_2-$,

(v)  or 

(w) $-\overset{\overset{\textstyle OR^{14}}{|}}{C}H-$,

(x) $-\overset{\overset{\textstyle OCOR^{16}}{|}}{C}H-$,

(y) $-\overset{\overset{\textstyle NR^{17}}{\|}}{C}-$, or

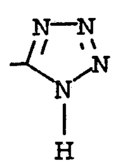
(z) $R^{18}O\quad OR^{19}$ $\diagdown\;\diagup$ $-C-$;

Z is O, NR^{13} or S;

r is 1 or 2; and

2. The compound of Claim 1 where K is O.

3. The compound of Claim 2 wherein:

R^1 is, $-COOH$ , $-NH-SO_2CF_3$,

$-SO_2NH-CO-R^{23}$, $-SO_2NH$-heteroaryl, $-SO_2NH$-aryl or $-CONHSO_2R^{23}$

R^{2a} and R^{2b} are H, F, Cl, CF_3, C_1-C_4-alkyl or C_1-C_4-alkoxy;

R^{3a} is H, F or Cl;

R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_1-C_4-alkoxy, $-COOCH_3$, $-COOC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1$-C_4-alkyl$)_2$ or $-NH-SO_2CH_3$;

E is a single bond, -O- or -S-;

R^6 is

(a) C_1-C_5-alkyl either unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF_3, CCl_3, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$ or phenyl;

(b) C_2-C_5-alkenyl or C_2-C_5-alkynyl;

X is a C-C single bond; and,

r is one.

4. The compound of Claim 3 wherein:

E is a single bond or -S-;

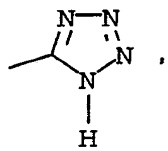
r is one,

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H;

R^6 is n-propyl, n-butyl, $-CH_3$, $-CH_2CH_3$, or $-CH_2-S-CH_3$;

R^8 is $-CO_2R^5$, $-CONHSO_2$aryl, $-CONHSO_2-(C_1$-C_4-alkyl), $-CONHSO_2$-cyclopropyl, $-HNSO_2(C_1$-C_4- polyfluoroalkyl), $-S(O)_x-(C_1$-C_4- alkyl)-aryl, $-NHSO_2$-aryl or $-NHSO_2$-heteroaryl;

R^1 is -COOH, SO_2NH-heteroaryl, -SO_2NH-aryl



-NH-SO_2-CF_3, or -SO_2NHCOR^{23};

R^{23} is aryl, -N(aryl)$_2$, C_3-C_7-cycloalkyl, C_1-C_6 alkyl, either unsubstituted or substituted with 1) C_3-C_7 cycloalkyl, 2) polyfluoro, or 3) two aryl groups, and

X is a single bond.

5. The compound of Claim 4 which is a member of the group:

(1) Ethyl 3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]isoxazole-5-carboxylate

(2) 3-Butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]isoxazole-5-carboxylic acid

(3) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-butylisoxazole-5-carboxylic acid

(4) 3-Butyl-4-[[2'-[N-(trifluoroacetyl)sulfamoyl]biphenyl-4-yl]methyl]isoxazole-5-carboxylic acid

(5) 3-Butyl-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isoxazole-5-carboxylic acid

(6) 3-Butyl-4-[[2'-[N-(cyclopropanecarbonyl)-sulfamoyl]biphenyl-4-yl]methyl]isoxazole-5-carboxylic acid

(7) 4-[[2'-[N-(Diphenylacetyl)sulfamoyl]-biphenyl-4-yl]methyl]-3-propylisoxazole-5-carboxylic acid

(8) 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]isoxazole-5-carboxylic acid

(9) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-propylisoxazole-5-carboxylic acid

(10) 4-[[2'-[N-(Cyclopropanecarbonyl)sulfamoyl]-biphenyl-4-yl]methyl]-3-propylisoxazole-5-carboxylic acid

(11) 3-Propyl-4-[[2'-(trifluoromethanesulfon-amido)biphenyl-4-yl]methyl]isoxazole-5-carboxylic acid

(12) 5-[N-(Benzenesulfonyl)carbamoyl]-3-butyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isoxazole

(13) 3-Butyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-isoxazole

(14) 3-Butyl-5-(pentafluoroethanesulfonamido)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isoxazole

(15) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-butyl-5-(trifluoromethanesulfon-amido)isoxazole

(16) 3-Butyl-4-[[2'-[N-(cyclopropanecarbonyl)-sulfamoyl]biphenyl-4-yl]methyl-5-(trifluoro-methanesulfonamido)isoxazole

(17) 3-Butyl-5-(trifluoromethanesulfonamido)-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isoxazole

(18) 3-Propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-isoxazole

(19) 5-(Pentafluoroethanesulfonamido)-3-propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isoxazole

(20) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-propyl-5-(trifluoromethanesulfon-amido)isoxazole

(21) 4-[[2'-[N-(Cyclopropanecarbonyl)sulfamoyl]-biphenyl-4-yl]methyl]-3-propyl-5-(trifluoro-methanesulfonamido)isoxazole

(22) 3-Butyl-5-(4-chlorobenzylsulfinyl)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isoxazole

(23) 3-Butyl-5-(2-carboxybenzylthio)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isoxazole

(24) 3-Butyl-5-[N-(isopropylsulfonyl)carbamoyl]-4-[[2'-(tetrazolyl)biphenyl-4-yl]methyl]-isoxazole

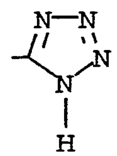
(25) 3-Butyl-5-[N-(cyclopropanesulfonyl)car-bamoyl]-4-[[2'-(tetrazolyl)biphenyl-4-yl]-methyl]isoxazole

(26) 3-Butyl-5-(4-fluorobenzenesulfonamido)-4-[[2'-(tetrazolyl)biphenyl-4-yl]methyl]-isoxazole

(27) 3-Butyl-5-(3-pyridinesulfonamido)-4-[[2'-(tetrazolyl)biphenyl-4-yl]methyl]-isoxazole

6. The compound of Claim 1 wherein K is S.

7. The compound of Claim 6 wherein:

R^1 is,  , $-NH-SO_2CF_3$, CO_2H

$-SO_2NHCOR^{23}$, $-SO_2NH$-heteroaryl, $-SO_2NH$-aryl or $-CONHSO_2R^{23}$;

R^{2a} and R^{2b} are H, F, Cl, CF_3, C_1-C_4-alkyl or C_1-C_4-alkoxy;

R^{3a} is H, F or Cl;

R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_5-C_6-cycloalkyl, $-COOCH_3$, $-COOC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1$-C_4-alkyl$)_2$ or $-NH-SO_2CH_3$;

E is a single bond, -O- or -S-;

R^6 is

(a) C_1-C_5-alkyl either unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF_3, CCl_3, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$ or phenyl;

(b) C_2-C_5-alkenyl or C_2-C_5-alkynyl;

X is a C-C single bond; and,

r is one.

8. The compound of Claim 7 wherein:

E is a single bond or -S-;

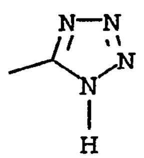
r is one,

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H;

R^6 is n-propyl, n-butyl, $-CH_3$, $-CH_2CH_3$, or $-CH_2-S-CH_3$;

R^8 is $-CO_2R^5$, $-CONHSO_2$aryl, $-CONHSO_2-(C_1-C_4$-alkyl), $-CONHSO_2$-cyclopropyl, $-NHSO_2(C_1-C_4$- polyfluoroalkyl) $(S(O)_x-(C_1-C_4$- alkyl)aryl, $-NHSO_2$-aryl or $-NHSO_2$-heteroaryl;

R^1 is, -COOH, $-SO_2$NH-heteroaryl, $-SO_2$NH-aryl



$NH-SO_2-CF_3$, or $-SO_2NHCOR^{23}$;

R^{23} is aryl, polyfluoro-C_1-C_4 alkyl, C_3-C_7 cycloalkyl or C_1-C_4 alkyl(aryl)$_2$; and

X is a single bond.

9. The compound of Claim 8 which is:

(1) Ethyl 3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]isothiazole-5-carboxylate

(2) 3-Butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]isothiazole-5-carboxylic acid

(3) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-butylisothiazole-5-carboxylic acid

(4) 3-Butyl-4-[[2'-[N-(trifluoroacetyl)sulfamoyl]-biphenyl-4-yl]methyl]isothiazole-5-carboxylic acid

(5) 3-Butyl-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isothiazole-5-carboxylic acid

(6) 3-Butyl-4-[[2'-[N-(cyclopropanecarbonyl)-sulfamoyl]biphenyl-4-yl]methyl]isothiazole-5-carboxylic acid

(7) 4-[[2'-[N-(Diphenylacetyl)sulfamoyl]biphenyl-4-yl]methyl]-3-propylisothiazole-5-carboxylic acid

(8) 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]isothiazole-5-carboxylic acid

(9) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-propylisothiazole-5-carboxylic acid

(10) 4-[[2'-[N-(Cyclopropanecarbonyl)sulfamoyl]-biphenyl-4-yl]methyl]-3-propylisothiazole-5-carboxylic acid

(11) 3-Propyl-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isothiazole-5-carboxylic acid

(12) 5-[N-(Benzenesulfonyl)carbamoyl]-3-butyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isothiazole

(13) 3-Butyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-isothiazole

(14) 3-Butyl-5-(pentafluoroethanesulfonamide)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isothiazole

(15) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-butyl-5-(trifluoromethanesulfon-amido)isothiazole

(16) 3-Butyl-4-[[2'-[N-(cyclopropanecarbonyl)-sulfamoyl]biphenyl-4-yl]methyl-5-(trifluoro-methanesulfonamide)isothiazole

(17) 3-Butyl-5-(trifluoromethanesulfonamido)-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]isothiazole

(18) 3-Propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-isothiazole

(19) 5-(Pentafluoroethanesulfonamido)-3-propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isothiazole

(20) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-propyl-5-(trifluoromethanesulfon-amido)isothiazole

(21) 4-[[2'-[N-(Cyclopropanecarbonyl)sulfamoyl]-biphenyl-4-yl]methyl]-3-propyl-5-(trifluoro-methanesulfonamido)isothiazole

(22) 3-Butyl-5-(4-chlorobenzylsulfinyl)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isothiazole

(23) 3-Butyl-5-(2-carboxybenzylthio)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-isothiazole

(24) 3-Butyl-5-[N-(isopropylsulfonyl)carbamoyl]-4-[[2'-(tetrazolyl)biphenyl-4-yl]methyl]-isothiazole

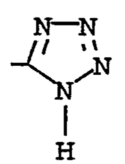
(25) 3-Butyl-5-[N-(cyclopropanesulfonyl)carbamoyl]-4-[[2'-(tetrazolyl)biphenyl-4-yl]-methyl]-isothiazole

(26) 3-Butyl-5-(4-fluorobenzenesulfonamido)-4-[[2'-(tetrazolyl)biphenyl-4-yl]methyl]-isothiazole

(27) 3-Butyl-5-(3-pyridinesulfonamido)-4-[[2'-(tetrazolyl)biphenyl-4-yl]methyl]-isothiazole

10. The compound 1 wherein K is NR^7.

11. The compound of Claim 10 wherein:

R^1 is -COOH,  , $-NH-SO_2CF_3$,

$-SO_2NHCOR^{23}$, $-SO_2NH$ heteroaryl, $-SO_2NH$-aryl, $-CONHSO_2R^{23}$;

R^{2a} and R^{2b} are H, F, Cl, CF_3, C_1-C_4-alkyl or C_1-C_4-alkoxy;

R^{3a} is H, F or Cl;

R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_5-C_6-cycloalkyl, $-COOCH_3$, $-COOC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1$-C_4-alkyl$)_2$ or $-NH-SO_2CH_3$;

E is a single bond, -O- or -S-;

R^6 is

(a) C_1-C_5-alkyl either unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF_3, CCl_3, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$ or phenyl;

(b) C_2-C_5-alkenyl or C_2-C_5-alkynyl;

R^7 and R^8 are as defined above;

X is a C-C single bond; and,

r is one.

12. The compound of Claim 11 wherein

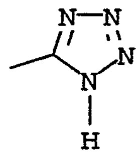
E is a single bond or -S-;

r is one,

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H;

R^6 is n-propyl, n-butyl, $-CH_3$, $-CH_2CH_3$, or $-CH_2-S-CH_3$;

R^1 is -COOH, $-SO_2NH$-heteroaryl, $-SO_2NH$-aryl $-CONHSO_2R^{23}$, $-SO_2NHSO_2R^{23}$

 ,

	$-NH-SO_2-CF_3$, $-SO_2NHCOR^{23}$, and
R^7 is	H, aryl-C_1-C_{10}-alkyl, polyfluoro-C_1-C_4-alkyl, heteroaryl, or aryl either unsubstituted or substituted with one or two substituents selected from -Cl, $-CF_3$, $-CH_3$, $-OCH_3$ and $-NO_2$;
R^8 is	$-CO_2R^5$, $-CONHSO_2$aryl, $-CONHSO_2$-(C_1-C_4-alkyl), $-CONHSO_2$-cyclopropyl, $-NHSO_2$(C_1-C_4 polyfluoroalkyl), $-S(O)_x$-(C_1-C_4-alkyl)-aryl $-NHSO_2$-aryl or $-NHSO_2$-heteroaryl;
R^{23} is	aryl, $-N(aryl)_2$, C_3-C_7-cycloalkyl, C_1-C_6 alkyl, either unsubstituted or substituted with 1) C_3-C_7 cycloalkyl, 2) polyfluoro, or 3) two aryl groups, and
X is	a single bond.

13. The compound of Claim 12 which is a member of the group selected from:

(1) 5-Amino-3-butyl-4-[(2'-carboxybiphen-4-yl)-methyl]-1-phenylpyrazole;

(2) 5-Amino-3-butyl-1-phenyl-4-[(2'-(tetrazol-5-yl)-biphen040yl)methyl]pyrazole;

(3) 3-Butyl-5-hydroxy-1-phenyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(4) 3-Butyl-5-carboxy-1-phenyl-4-'[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(5) 3-Butyl-5-carbomethoxy-1-phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(6) 3-Butyl-5-hydroxymethyl-1-phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(7) 3-Butyl-1-(2-chloro)phenyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-5-hydroxymethyl-pyrazole;

(8) 1-(2-Chloro)phenyl-5-hydroxymethyl-3-propyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(9) 3-Butyl-5-carboxy-1-(2-chloro)phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(10) 3-Butyl-5-carbomethoxy-1-(2-methyl)phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(11) 3-Butyl-5-carbomethoxy-1-(2-nitro)phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(12) 3-Butyl-5-carbomethoxy-1-(2-trifluoromethyl)-phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-pyrazole;

(13) 3-Butyl-5-carbomethoxy-1-(2-chloro-4-methoxy)-phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-pyrazole;

(14) 3-Butyl-5-carbomethoxy-1-propyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(15) 3-Butyl-5-carbomethoxy-1-isobutyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(16) 3-Butyl-5-carbomethoxy-1-pentafluoroethyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(17) 3-Butyl-5-carbomethoxy-1-cyclohexylmethyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(18) 3-Butyl-5-carbomethoxy-1-dimethylaminomethyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(19) 3-Butyl-5-acetamido-1-(2-chloro)phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(20) 3-Butyl-1-(2-chloro)phenyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-5-trifluoromethylsulfonamidopyrazole;

(21) 3-Butyl-1-(2-chloro)phenyl-5-dimethylamino-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(22) 3-Butyl-1-(2-chloro)phenyl-5-propylamino-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(23) 3-Butyl-1-(2-chloro)phenyl-5-methoxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(24) 3-Butyl-1-(2-chloro)phenyl-5-propyloxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(25) 3-Butyl-1-(2-chloro)phenyl-5-methylsulfinyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(26) 3-Butyl-1-(2-chloro)phenyl-5-methylsulfonyl-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(27) 3-Butyl-1-(2-(trifluoromethyl)phenyl)-5-carboxy-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(28) 3-Butyl-1-(2-(trifluoromethyl)phenyl)-5-carbethoxy-4-[(2'-(N-cyclopropanecarbonyl)-sulfonamidobiphen-4-yl)methyl]pyrazole;

(29) 3-Butyl-1-(2-(trifluoromethyl)phenyl)-5-trifluoromethanesulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(30) 3-Butyl-1-(2-(trifluoromethyl)phenyl)-5-pentafluoromethanesulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(31) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-carboxy-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(32) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-carboethoxy-4-[(2'-(N-cyclopropanecarbonyl)-sulfonamidobiphen-4-yl)methyl]pyrazole;

(33) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-trifluoromethanesulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(34) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-pentafluoroethanesulfonamidosulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)-methyl]pyrazole;

(35) 3-Butyl-1-(2,6-dichlorophenyl)-5-carboxy-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)-methyl]pyrazole;

(36) 3-Butyl-1-(2,6-dichlorophenyl)-5-carboethoxy-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)-methyl]pyrazole;

(37) 3-Butyl-1-(2,6-dichlorophenyl)-5-trifluoromethanesulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(38) 3-Butyl-1-(2,6-dichlorophenyl)-5-pentafluoroethanesulfonamido-4-[(2'-(N-cyclopropanecarbonyl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(39) 3-Butyl-1-(trifluoromethyl)phenyl)-5-carboxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(40) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-carboethoxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(41) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-trifluoromethanesulfonamido-4-[(2'-(N-butyryl)-sulfonamidobiphen-4-yl)methyl]-pyrazole;

(42) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-pentafluoroethanesulfonamido-4-[(2'-(N-butyryl)-sulfonamidobiphen-4-yl)methyl]-pyrazole;

(43) 3-Propyl-1-(2-(trifluoromethyl)phenyl-5-carboxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(44) 3-Propyl-1-(2-(trifluoromethyl)phenyl-5-carboethoxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(45) 3-Propyl-1-(2-(trifluoromethyl)phenyl-5-trifluoromethanesulfonamido-4-[(2'-(N-butyryl)-sulfonamidobiphen-4-yl)methyl]-pyrazole;

(46) 3-Propyl-1-(2-(trifluoromethyl)phenyl-5-pentafluoroethanesulfonamido-4-[(2'-(N-butyryl)-sulfonamidobiphen-4-yl)methyl]-pyrazole;

(47) 3-Butyl-1-(2,6-(dichlorophenyl)-5-carboxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(48) 3-Butyl-1-(2,6-(dichlorophenyl)-5-carboethoxy-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]-pyrazole;

(49) 3-Butyl-1-(2,6-(dichlorophenyl)-5-trifluoromethanesulfonamido-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(50) 3-Butyl-1-(2,6-(dichlorophenyl)-5-pentafluoroethanesulfonamido-4-[(2'-(N-butyryl)sulfonamidobiphen-4-yl)methyl]pyrazole;

(51) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-carboxy--4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-pyrazole;

(52) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-carboethoxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrazole;

(53) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-trifluoromethanesulfonamido-4-[(2'-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrazole;

(54) 3-Butyl-1-(2-(trifluoromethyl)phenyl-5-pentafluoroethanesulfonamido-4-[(2'-(tetrazol-5-yl)-biphen-4-yl)methyl]pyrazole;

(55) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-carboxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrazole;

(56) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-carboethoxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)-methyl]pyrazole;

(57) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-trifluoromethanesulfonamido-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(58) 3-Propyl-1-(2-(trifluoromethyl)phenyl)-5-pentafluoroethanesulfonamido-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(59) 3-Butyl-1-(2,6-dichlorophenyl)-5-carboxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(60) 3-Butyl-1-(2,6-dichlorophenyl)-5-carboethoxy-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(61) 3-Butyl-1-(2,6-dichlorophenyl)-5-trifluoromethanesulfonamido-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(62) 3-Butyl-1-(2,6-dichlorophenyl)-5-pentafluoroethanesulfonamido-4-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]pyrazole;

(63) Ethyl 3-butyl-1-(2,4-dichlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(64) 3-Butyl-1-(2,4-dichlorophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(65) Ethyl 3-butyl-1-(4-methoxyphenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(66) 3-Butyl-1-(4-methoxyphenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(67) Ethyl 3-butyl-1-(2-nitrophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(68) 3-Butyl-1-(2-nitrophenyl)-4-[[2'-(5-tetrazolyl)-biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(69) Ethyl 3-butyl-1-(4-methoxy-2-nitrophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(70) 3-Butyl-1-(4-methoxy-2-nitrophenyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(71) 3-Butyl-1-(2-pyridyl)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(72) 1-Benzyl-3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(73) Ethyl 1-(2-chlorophenyl)-3-propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(74) 1-(2-Chlorophenyl)-3-propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(75) 1-(2,6-Dichlorophenyl)-3-propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(76) Ethyl 3-propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylate

(77) 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylic acid

(78) Ethyl 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-(trifluoroethyl)-1H-pyrazole-5-carboxylate

(79) 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]-1-(2,2,2-(trifluoroethyl)-1H-pyrazole-5-carboxylic acid

(80) Ethyl 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylate

(81) 3-Propyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]-methyl]-1H-pyrazole-5-carboxylic acid

(82) 3-Butyl-1-(2-chlorophenyl)-4-[[2'-[N-(cyclopropanecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(83) 3-Butyl-1-(2,6-dichlorophenyl)-4-[[2'-[N-isobutyrylsulfamoyl]biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(84) 3-Butyl-4-[[2'-[N-(3-cyclopentylpropionyl)sulfamoyl]biphenyl-4-yl]methyl]-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole-5-carboxylic acid

(85) 3-Butyl-4-[[2'-[N-(diphenylacetyl)sulfamoyl]biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(86) 4-[[2'-[N-(N,N-diphenylcarbamoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-propyl-1H-pyrazole-5-carboxylic acid

(87) 4-[[2'-[N-(Diphenylacetyl)sulfamoyl]biphenyl-4-yl]methyl]-3-propyl-1H-pyrazole-5-carboxylic acid

(88) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]methyl]-1-(2-chlorophenyl)-3-propyl-1H-pyrazole-5-carboxylic acid

(89) 1-(2,6-Dichlorophenyl)-3-propyl-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

(90) 3-Butyl-4-[[2'-[N-(pyrimidin-2-yl)sulfamoyl]biphenyl-4-yl]methyl]-1-[2-(trifluoromethyl)-phenyl]-1H-pyrazole-5-carboxylic acid

(91) 4-[[2'-[N-(4-Nitrophenyl)sulfamoyl]biphenyl-4-yl]methyl]-3-propyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxylic acid

(92) 4-[[2'-[N-(Diphenylacetyl)sulfamoyl]biphenyl-4-yl]methyl]-3-ethyl-1H-pyrazole-5-carboxylic acid

(93) 3-Butyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-1-(2,6-dichlorophenyl)-1H-pyrazole-5-carboxylic acid

(94) 4-[[2'-[N-(Benzenesulfonyl)carbamoyl]biphenyl-4-yl]methyl]-3-butyl-1-(2-chlorophenyl)-1H-pyrazole-5-carboxylic acid

(95) 5-[N-(Benzenesulfonyl)carbamoyl]-3-butyl-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole

(96) 3-Butyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]-methyl]-5-(trifluoromethanesulfonamido)-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole

(97) 3-Butyl-1-(2-chlorophenyl)-5-(pentafluoro-ethanesulfonamido)-4-[[2'-(tetrazol-5-yl)-biphenyl-4-yl]methyl]-1H-pyrazole

(98) 3-Butyl-5-(pentafluoroethanesulfonamido)-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-1-[2-(tri-fluoromethyl)phenyl]-1H-pyrazole

(99) 4-[[2'-[N-(Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-butyl-1-[2-(chlorophenyl)-5-(tri-fluoromethanesulfonamido)1H-pyrazole

(100) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]methyl]-3-butyl-5-(trifluoromethanesulfonamido)-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole

(101) 3-Butyl-1-(2-chlorophenyl)-4-[[2'-[N-(cyclopro-panecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-1H-pyrazole

(102) 3-Butyl-1-(2-chlorophenyl)-4-[[2'-[N-(cyclopro-panecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-(pentafluoroethanesulfonamido)-1H-pyrazole

(103) 3-Butyl-4-[[2'-[N(cyclopropanecarbonyl)sulfamo-yl]biphenyl-4-yl]methyl]-5-(trifluoromethane-sulfonamido)-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole

(104) 1-(2-Chlorophenyl)-3-propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-5-(trifluoromethanesulfonamido)-1H-pyrazole

(105) 3-Propyl-4-[[2'-(tetrazol-5-yl)biphenyl-4-yl]-methyl]-5-(trifluoromethanesulfonamido)-1-[2-(trifluoromethyl)phenyl-1H-pyrazole

(106) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-1-(2-chlorophenyl)-3-propyl-5-(trifluoromethanesulfonamido)-1H-pyrazole

(107) 4-[[2'-(N-Benzoylsulfamoyl)biphenyl-4-yl]-methyl]-3-propyl-5-(trifluoromethanesulfonamido)-1-[2-(trifluoromethyl)phenyl]-1H-pyrazole

(108) 1-(2-Chlorophenyl)-4-[[2'-[N-(cyclopropanecarbonyl)sulfamonyl]biphenyl-4-yl]methyl]-3-propyl-5-(trifluoromethanesulfonamido)-1H-pyrazole

(109) 4-[[2'-[N-(Cyclopropanecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-3-propyl-5-(trifluoromethanesulfonamido)-1-[2-(trifluoromethyl)-phenyl]-1H-pyrazole

(110) 1-(2-Chlorophenyl)-4-[[2'-[N-(cyclopropanecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-(pentafluoroethanesulfonamido)-3-propyl-1H-pyrazole

(111) 1-(2-Chlorophenyl)-5-(pentafluoroethanesulfonamido)-3-propyl-4-[[2'-(tetrazol-5-yl)-biphenyl-4-yl]methyl]-1H-pyrazole

(112) 3-Butyl-1-(2-chlorophenyl)-5-(trifluoromethanesulfonamido)-4-[[2'-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]-1H-pyrazole.

(113) 3-Butyl-5-[N-(isopropylsulfonyl)carbamoyl]-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole

(114) 3-Butyl-5-[N-(cyclopropanesulfonyl)carbamoyl]-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole

(115) 3-Butyl-5-(pyridinesulfonamido)-4-[[2'-(5-tetrazolyl)biphenyl-4-yl]methyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole

14. A pharmaceutical composition useful in the treatment of hypertension which comprises a therapeutically acceptable carrier and a pharmaceutically effective amount of a compound of Claim 1.

15. The composition of Claim 11 which includes in addition another antihypertensive agent selected from a diuretic or a β-blocker or an angiotensin converting enzyme inhibitor or a calcium channel blocker which is a member selected from the group consisting of: amiloride, atenolol, bendroflumethiazide, chlorothalidone, chlorothiazide, clonidine, cryptenamine acetates and cryptenamide tannates, deserpidine, diazoxide, guanethidine sulfate, hydralazine hydrochloride, hydrochlorothiazide, metolazone, metoprolol tartate, methyclothiazide, methyldopa, methyldopate hydrochloride, minoxidil, pargyline hydrochloride, polythiazide, prazosin, propranolol, rauwolfia serpentina, rescinnamine, reserpine, sodium

nitroprusside, spironolactone, timolol maleate, trichlormethiazide, trimethophan camsylate, benzthiazide, quinethazone, ticrynafan, triamterene, acetazolamide, aminophylline, cyclothiazide, ethacrynic acid, furosemide, merethoxylline procaine, sodium ethacrynate, captopril, delapril hydrochloride, enalapril, enalaprilat, fosinopril sodium, lisinopril, pentopril, quinapril hydrochloride, ramapril, teprotide, zofenopril calcium, diflusinal, diltiazem, felodipine, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine, as well as admixtures and combinations thereof.

16. A method of treating hypertension which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of Claim 1.

17. An ophthalmological formulation for the treatment of ocular hypertension comprising an ophthalmologically acceptable carrier and a therapeutically effective amount of a compound of Claim 1.

18. A method of treating ocular hypertension comprising administering to a patient in need of such treatment therapeutically effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/01952

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C07D 261/08

US CL.: 548/247

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
US	548/247

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

Chemical Abstracts - CAS ON LINE

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4,230,826 (LIU et al.) 28 October 1980 Note column 1, lines 15.	1-3

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24 JUNE 1990	11 JUL 1991
International Searching Authority	**Signature of Authorized Officer**
ISA/US	ROBERT W. RAMSUER

Form PCT/ISA/210 (second sheet) (Rev.11-87)

International Application No. PCT/US91/01952

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ **OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE** [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers , because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☒ Claim numbers 1-18 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

See extra sheet.

3. ☐ Claim numbers__________, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ **OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING** [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

The claims were found unsearchable because of the multitude of variables and their permutations and combinations (e.g. K, R^1-R^8 etc.) result in claims that are so broad in scope that they are rendered virtually incomprehensible and thus no meaningful search can be given. Therefore the first discernable invention as found in the claims (1-3) i.e. that wherein K is O, R^1 is COOH, R^{2a} is H, C_1-C_4 alkyl, R^{2b} is H, C_1-C_6 alkyl, R^{3b} is H, C_1-C_6 alkyl, X is a direct bond, R^6 is C_1-C_6 alkyl, E is a single bond, and R^8 is H, has been searched.